The Health Consequences Of Smoking

CARDIOVASCULAR DISEASE

a report of the Surgeon General

1983

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TO THE READERS OF THIS VOLUME:

Provisions of the Public Health Cigarette Smoking Act of 1969 (P.L. 91-222) require the Secretary of Health and Human Services to submit an annual report to the Congress on the health consequences of smoking. Attached is the 1983 report, Health Consequences of Smoking: Cardiovascular Disease. This volume is an indepth analysis of the scientific evidence of the relationship between cigarette smoking and multiple cardiovascular diseases. This relationship is quantitatively the most serious of the health consequences of smoking, but is poorly recognized by the public.

This report represents the consolidated work of many widely-recognized experts known for their contribution to understanding cardiovascular disease. It is a scientific reference document to serve as a state-of-the-art source for medical and behavioral scientists and researchers.

Smoking-related cardiovascular disease is estimated to account for more deaths than any other smoking-related disease, including cancer. This report clearly establishes that cigarette smoking increases the risks for a number of cardiovascular diseases, particularly coronary heart disease, the largest single cause of deaths in the United States. In addition, smoking is related to an increased risk for stroke, atherosclerosis, and other circulatory diseases.

The report clearly demonstrates that cigarette smoking is a major risk factor for coronary heart disease in the United States. There are 55 million persons who smoke, a larger population than those who have hypertension or elevated cholesterol, the other major risk factors for this disease. Smokers' death rates from coronary heart disease are 70 percent greater than those of non-smokers. Simply by quitting smoking, these men and women dramatically reduce their risk of premature death from this disease.

The economic and social toll these smoking-related deaths extract from the Nation's health is immeasurable. The report's findings re-emphasize the importance of this Department's continued educational efforts to enable a fully-informed choice by individuals on whether to begin or to continue to smoke.

In my view, this volume is a solid scientific work and a contribution to the prevention efforts of this Department.

Margaret M. Heckler

Margaret M. Heckler
Secretary

FOREWORD

The 1983 Report is the second volume in *The Health Consequences of Smoking* series that focuses on specific diseases. The 1982 Report reviewed in depth the association between tobacco use and various cancers; the 1983 Report is a comprehensive review of the relationship between smoking and cardiovascular disease.

The ability to draw a conclusion from the scientific evidence on the causal relationship between smoking and cardiovascular disease was reached more recently than it was from the evidence on the relationship between smoking and cancer. The latter relationship was first established scientifically 30 years ago, particularly for lung cancer. At the time the Advisory Committee on Smoking and Health was formed in 1962, the scientific evidence linking tobacco use, particularly cigarettes, with respiratory cancers was overwhelming. A causal link between cigarette use and lung cancer was both clear and compelling. A number of epidemiological studies on the relationship between smoking and coronary heart disease (CHD) existed at that time, but the Committee felt that the evidence was insufficient to make a judgment of a causal relationship.

Nevertheless, the Committee found the evidence compelling enough to caution that even though the causal role of cigarette smoking in coronary heart disease was not proved, countermeasures were warranted, and the Committee counseled against postponing action until no uncertainty remained. The evidence was reviewed again in the 1971 Surgeon General's Report and was, by this time, clearly strong enough to establish cigarette smoking as a major risk factor for coronary heart disease in men. By 1979, when the 15th year anniversary Report of the Surgeon General was published, there was no longer any doubt that cigarette smoking was directly related to coronary heart disease for both men and women in the United States.

The Importance of Cardiovascular Disease

The importance of cardiovascular disease, particularly coronary heart disease, to the health of the American public is evident. In 1980 cardiovascular disease accounted for approximately half of all U.S. deaths—960,000 out of 1,980,000 total deaths. Of these, slightly

over 565,000 were due to coronary heart disease; that is, approximately 30 percent of all deaths and almost 60 percent of all cardiovascular deaths were due to CHD. The age-adjusted CHD death rate peaked in 1963, and by 1980 had declined 30 percent. In the period between 1968 and 1978 alone, the age-adjusted rate declined 26.5 percent, with a greater decline noted for the younger age groups.

In comparison, the total number of all cancer deaths was slightly over 416,000 in 1980. Thus, deaths from CHD exceeded all cancer deaths, and deaths from all cancers numbered less than one-half the total of all cardiovascular deaths.

Last year this Department issued a report in which it was estimated that tobacco use, particularly cigarette smoking, was related to 30 percent of all cancer deaths in the United States—a projected 129,000 premature deaths. The findings of this year's Report, however, should be considered even more alarming, in that the number of cardiovascular deaths that are reasonably estimated to be cigarette related is even higher. A number of investigators[1] have estimated that 30 percent, or more, of CHD deaths could be attributed to cigarette smoking because of the higher CHD death rates experienced by eversmokers compared with neversmokers. If 30 percent of coronary heart disease deaths are attributed to cigarette smoking, 170,000 Americans will die prematurely of CHD each year. Smokers also experience increased death rates owing to other cardiovascular diseases such as stroke, peripheral vascular disease, aortic atherosclerosis, and other vascular problems.

Findings of the 1983 Report—Coronary Heart Disease and Cigarette Smoking

Each of the three major risk factors poses approximately the same increase in risk of CHD for the person with the risk factor, but cigarette smoking is far more prevalent as a risk factor for CHD in the American population than either hypertension or elevated serum cholesterol. Thus, the overall finding of this Report is clear: **Cigarette smoking should be considered the most important of the known modifiable risk factors for coronary heart disease in the United States.**

For over 25 years, cigarette smoking has been linked epidemiologically with an increased risk of dying from coronary heart disease. As early as 1954, a strong, statistically significant association between cigarette use and CHD was demonstrated. In the intervening years, additional studies have confirmed this association. An examination of only the major prospective studies, involving more than 20 million

[1]Report of the Royal College of Physicians, London, 1978; Rogot and Murray, Public Health Reports, 1980; Garfinkel, Proceedings of the Fourth World Conference on Smoking and Health, Stockholm, 1980. See Section 3 for additional discussion.

person-years of observation, indicates that smoking has been consistently shown to elevate CHD mortality rates. Overall, smokers have a 70 percent greater CHD mortality than nonsmokers. Heavy smokers, those who consume more than two packs per day, experience CHD mortality rates almost 200 percent greater than nonsmokers.

In the National Pooling Project study, a unique study that combined data from five of the Nation's largest incidence studies on heart disease, smokers of a pack or more per day were found to have a greater than 2.5-fold increased risk of developing a major coronary event compared with nonsmokers. This study also found that smokers who have other major risk factors experience a greater increased risk than would be expected from the summation of the independent risks. Thus, cigarette smoking interacts with the other major risk factors in a manner that greatly increases the risk of CHD.

The risk of developing and dying from CHD is directly related to the total dosage of cigarette smoke exposure. A dose–response relationship has been established for the number of cigarettes smoked per day, the total years of cigarette smoking, and the degree of inhalation; CHD risk is inversely related to the age of initiation. CHD mortality ratios are also greater at the younger age groups; thus, preventive efforts could truly have a decided impact on extending life-expectancy—if large numbers of smokers could be persuaded to quit smoking. The decrease in elevated CHD risk with cessation, coupled with the prevalence of smoking as a risk factor in the U.S. population, means that the elimination of cigarette usage could have a greater impact on CHD morbidity and mortality than any other preventive measure.

Sudden Cardiac Death

Smokers are at a two to four times greater risk for sudden cardiac death (SCD) than are nonsmokers. The risk for sudden death increases with increasing daily exposure, as measured by the number of cigarettes consumed per day.

Stroke

The association between cigarette smoking and cerebrovascular disease (CVD) is largely confined to the younger age groups, with little evidence of an effect after age 65. The number of stroke deaths in 1980 totaled 170,000; even a small percentage of such deaths represents thousands of premature deaths.

Women

For women who both smoke cigarettes and used oral contraceptives, a strong association exists between their use and one form of stroke—subarachnoid hemorrhage. Smoking and oral contraceptive use appear to interact synergistically to greatly increase the risk of subarachnoid hemorrhage and of CHD, compared with the risk for those women who neither smoke nor use oral contraceptives.

Other Cardiovascular Disease

Cigarette smoking contributes to the development of aortic atherosclerosis and arteriosclerotic peripheral vascular disease (APVD). Ninety percent of patients with APVD are cigarette smokers, and the successful management of this disease includes complete smoking cessation by such patients.

Changing Trends in Smoking Behavior and Coronary Heart Disease

Demographers have noted a reduction in mortality rates from heart disease for several years. However, a sharp decline in these rates occurred in the late 1960s for reasons that are not entirely known. Significantly, declines in cigarette smoking prevalence among adults were first noted in 1964, the year of the first Surgeon General's Report, with declines in prevalence accelerating between 1966 and 1970. By 1980, overall adult smoking prevalence had declined by nearly 25 percent. While the magnitude of the impact of these changes in smoking behavior on the decline in CHD death rates is uncertain, the direction and nature of that impact is not. The substantial changes in smoking behavior that have occurred over the last 20 years have exerted, and will continue to exert, a substantial beneficial effect on the incidence of CHD in the U.S. population.

We know from cohort mortality studies, incidence studies, and, more recently, intervention trials that smoking cessation results in a reduction in CHD mortality.

Data from the Multiple Risk Factor Intervention Trial (MRFIT) have shown that those cigarette smokers who reported quitting at their first-year interview (after an average of 6 years of followup) reduced their relative risk for CHD mortality by almost half compared with those smokers who continued to smoke. Mortality from all causes was almost 30 percent lower among those who quit smoking compared with those who continued to smoke. These data correlate well with those observed in the cohort mortality studies, which have consistently shown a decline in CHD mortality among former smokers compared with continuing smokers. In some studies

a substantial improvement in mortality within the first few years after smoking cessation was demonstrated.

Public Perception of the Scientific Link Between Cigarette Smoking and CHD

A recent staff report by the Federal Trade Commission revealed that a substantial proportion of the American public is not aware of the link between cigarette smoking and heart disease. When asked to respond to the statement "Cigarette smoking is a major cause of heart disease," 40 percent of adults responded "false" or "don't know," including almost half of the adult smokers (45 percent). This concurs with results from a 1980 Roper survey, which found that 53 percent of the population and 58 percent of smokers did not know that smoking causes *many* cases of heart attack; a surprising 20 percent were not even aware that smoking causes *some* cases.

It is apparent that for a significant segment of the general public, a large gap exists in its understanding of the relationship between cigarette smoking and heart disease, a relationship that accounts for the largest number of excess deaths of all the diseases associated with cigarette smoking.

In last year's Report, I stated that the education of our citizens regarding the health hazards of smoking cannot be left solely to government. The findings of this Report and previous ones compel me again to ask for an increased commitment by the health care community, voluntary health agencies, schools, and other groups in our society to join this Department and the Public Health Service in our continuing efforts to reduce the premature death and disability associated with cigarette smoking through renewed efforts of education and information.

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

PREFACE

In 1982, the Public Health Service's Report on the health consequences of smoking dealt with the relationship between smoking and cancer. This 1983 Report turns its attention to the relationship between cigarette smoking and cardiovascular disease, one that imposes an even greater burden of disease and premature death.

In preparing this Report, the Public Health Service has reviewed a world literature that goes back more than 40 years and has examined the results of epidemiological observations covering many millions of person-years. This evidence permits us to affirm again what was said in our 1979 Report and what is the consensus of other scientific bodies here and across the world. Cigarette smoking is causally related to heart disease; it and elevated levels of serum cholesterol and hypertension constitute the major risk factors for contracting and dying from this disease.

Since 1979, much additional information has accumulated to support this judgment. From a public health viewpoint, the most important is the new and further evidence presented in this volume that when one quits smoking, the risk of dying from heart disease begins to recede almost immediately and eventually becomes no greater than that experienced by someone who has never smoked at all. This is an encouragement to personal action and a justification for much greater research and program effort by government and voluntary agencies in helping people to quit smoking.

As in all previous Reports, the Public Health Service has turned to many people and agencies within the research and clinical community in developing this statement. On behalf of the Service, I express my respect and gratitude to them.

C. Everett Koop, M.D.
Surgeon General

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SECTION 1. INTRODUCTION, OVERVIEW, AND CONCLUSIONS

Introduction

Organization and Development of the 1983 Report

The content of the Report is the work of numerous scientists and experts within the Department of Health and Human Services as well as from outside the organization. Individual manuscripts were written by experts nationally and internationally recognized for their scientific contributions to the understanding of cardiovascular diseases. These manuscripts were reviewed individually by other experts, within and outside the U.S. Public Health Service, and the entire Report was reviewed by a broad-based panel of distinguished cardiovascular scientists. The 1983 Report includes a Foreword by the Assistant Secretary for Health of the Department of Health and Human Services and a Preface by the Surgeon General of the U.S. Public Health Service. The body of the report consists of eight sections and two appendices, as follows:

- Section 1. Introduction, Overview, and Conclusions
- Section 2. Arteriosclerosis
- Section 3. Coronary Heart Disease
- Section 4. Cerebrovascular Disease
- Section 5. Atherosclerotic Peripheral Vascular Disease and Aortic Aneurysm
- Section 6. Pharmacological and Toxicological Implications of Smoke Constituents on Cardiovascular Disease
- Section 7. Changes in Cigarette Smoking Behavior in Clinical and Community Trials
- Section 8. The Effect of Cigarette Smoking Cessation on Coronary Heart Disease
- Appendix A. Trends in Cardiovascular Diseases
- Appendix B. Trends in U.S. Cigarette Use, 1965 to 1980

Historical Perspective

Early reports linking smoking with a greater risk of developing cardiovascular disease occurred around the turn of the century. An early series of studies, initiated in 1904 by Erb, found a much higher percentage of smokers than of nonsmokers with intermittent claudication; only 10 percent of his patients with claudication were nonusers of tobacco. As early as 1934, Howard made the observation that the increasing prevalence of coronary heart disease noted since the first World War might be a result of the greatly increased use of cigarettes.

By the turn of the century, numerous studies had demonstrated clinically and experimentally that cigarette smoking or cigarette smoke constituents, most notably nicotine, caused an elevation in blood pressure and heart rate during smoking.

The first major prospective study results were made public in 1954 in the United States by Hammond and Horn and found a strong association between cigarette use among men and coronary heart disease (CHD). Overall, smokers were found to carry a 70 percent greater risk of dying from CHD than nonsmokers; heavy smokers had CHD mortality rates almost two and one-half times greater than nonsmokers. Hammond and Horn also noted a consistent dose–response relationship with the number of cigarettes consumed per day.

In the intervening 30 years, numerous additional epidemiological mortality studies were undertaken to examine this issue. These included studies in the United Kingdom, Canada, Sweden, Japan, and Switzerland in addition to the United States. In total, they represent more than 20 million person-years of observation. Findings from these studies have been remarkably uniform: smokers have much higher death rates from coronary heart disease than do nonsmokers, despite the fact that these studies were conducted in varying populations, were geographically diverse, and involved differing methodologies.

The first major U.S. Public Health Service review of the relationship between smoking and heart disease was conducted by the Surgeon General's Advisory Committee on Smoking and Health in 1964. Although the Committee noted that male smokers had higher death rates from coronary heart disease, it was unable to conclude that the association had causal significance. However, it was noted in the report that "the causative role of these factors [risk factors including cigarette smoking] in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgement until no uncertainty remains."

Since the release of the original Report of the Surgeon General in 1964, additional studies dealing with cigarette smoking and CHD have been summarized in the series of annual reports of the Surgeon General *The Health Consequences of Smoking*. By 1979, the magnitude of the epidemiological, pathological, clinical, and experimental evidence had grown to the point that the Surgeon General's Report concluded: "Smoking is causally related to coronary heart disease in the common sense of that idea and for the purposes of preventive medicine."

Overview

In 1980, diseases of the circulatory system were responsible for approximately one-half of the total U.S. mortality. *CHD was the*

single most important cause of death, accounting for approximately 30 percent of all U.S. deaths.

Cigarette smoking is one of the three major independent CHD risk factors. The magnitude of the risk associated with cigarette smoking is similar to that associated with the other two major CHD risk factors, hypertension and hypercholesterolemia; however, because cigarette smoking is present in a larger percentage of the U.S. population than either hypertension or hypercholesterolemia, cigarette smoking ranks as the largest preventable cause of CHD in the United States. Cigarette smoking also acts synergistically with the other major risk factors to greatly increase the risk for CHD.

Arteriosclerosis is the predominant underlying cause of cardiovascular disease, and atherosclerosis is the form of arteriosclerosis that most frequently causes clinically significant disease, including CHD, atherothrombotic brain infarction, atherosclerotic aortic disease, and atherosclerotic peripheral vascular disease. Cigarette smoking contributes both to the development of atherosclerotic lesions and to the clinical manifestations of atherosclerotic vascular disease, including sudden death. Although the precise pathophysiologic basis of these clinical manifestations is not understood, it may be related to several deleterious cardiovascular effects of cigarette smoking, including production of an imbalance between myocardial oxygen supply and demand, a decrease in the threshold for ventricular fibrillation, and an increase in platelet aggregation. Nicotine and carbon monoxide are the tobacco smoke constituents most closely associated with these adverse effects; other cigarette smoke constituents such as hydrogen cyanide, oxides of nitrogen, and carbon disulfide are being studied for possible pathogenic cardiovascular effects.

Cigarette smoking is the most important risk factor for atherosclerotic peripheral vascular disease, which usually involves the lower extremities. Smoking cessation is probably the single most important intervention in the management of this disorder. The effect of cigarette smoking to aggravate and accelerate the development of atherosclerosis is more striking in the aorta than in any other vessels. Cigarette smoking is associated with an increased risk for cerebrovascular disease, especially in younger age groups, but this effect is less marked than for atherosclerotic disease at other sites. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage; the use of both cigarettes and oral contraceptives greatly increases this risk.

Smoking cessation is associated with decreased mortality and morbidity from atherosclerotic vascular disease. Prospective epidemiologic studies have shown that former cigarette smokers reduce their CHD death risk from that of current smokers to that of nonsmokers over approximately a 15-year period after stopping

smoking. The beneficial effects of quitting are not explained by differences in baseline characteristics between quitters and continuing smokers. CHD intervention trials have successfully demonstrated the feasibility of reducing cigarette consumption; these trials also documented a significant reduction in CHD mortality.

Conclusions of the 1983 Report

The purpose of this Report is to review in depth the many sources of scientific evidence relating cigarette smoking to individual cardiovascular disease entities. Listed below are the major findings of this review.

Arteriosclerosis

1. A preponderance of evidence both from prospective studies with autopsy followup and from autopsy studies with retrospective smoking data indicates that cigarette smoking has a significant positive association with atherosclerosis. This evidence suggests that cigarette smoking has the effect of aggravating and accelerating the development of atherosclerotic lesions in the artery wall and that its effect is not limited to those events related to the occlusive episode. The effects are most striking for aortic atherosclerosis; a significant positive relationship also exists between cigarette smoking and atherosclerotic lesions in the coronary arteries, at least for most high risk populations. Cigarette smoking could also be associated with other factors that precipitate thrombosis, hemorrhage, or vasoconstriction leading to occlusion and ischemia.
2. Some evidence exists that cigarette smoke alters total serum cholesterol concentrations and lipoprotein composition in ways that would be expected to increase the development of atherosclerosis. Recent studies of the effects of smoking on the hemostatic system indicate effects on platelet function.
3. Although the specific mechanisms by which tobacco smoke affects arteriosclerosis have not been clearly delineated, the effects of cigarette smoking on the atherosclerotic lesions that underlie cardiovascular disease seem well established.

Coronary Heart Disease

1. Cigarette smoking is a major cause of coronary heart disease in the United States for both men and women. Because of the number of persons in the population who smoke and the increased risk that cigarette smoking represents, it should be considered the most important of the known modifiable risk factors for CHD.

2. Overall, cigarette smokers experience a 70 percent greater CHD death rate than do nonsmokers. Heavy smokers, those who consume two or more packs per day, have CHD death rates between two and three times greater than nonsmokers.
3. The risk of developing CHD increases with increasing exposure to cigarette smoke, as measured by the number of cigarettes smoked daily, the total number of years one has smoked, and the degree of inhalation, and with an early age of initiation.
4. Cigarette smokers have a twofold greater incidence of CHD than do nonsmokers, and heavy smokers have an almost fourfold greater incidence.
5. Cigarette smoking is a major independent risk factor for CHD, and it acts synergistically with other risk factors (most notably, elevated serum cholesterol and hypertension) to greatly increase the risk of CHD.
6. Women have lower rates for CHD than do men. In particular, CHD rates for women are lower prior to the menopause. A part of this difference is due to the lower prevalence of smoking in women, and for those women who do smoke, to the tendency to smoke fewer cigarettes per day and to inhale less deeply. Among those women who have smoking patterns comparable to male smoking patterns, the increments in CHD death rates are similar for the two sexes.
7. Women who use oral contraceptives and who smoke increase their risk of a myocardial infarction by an approximately tenfold factor, compared with women who neither use oral contraceptives nor smoke.
8. Cigarette smoking has been found to significantly elevate the risk of sudden death. Overall, smokers experience a two to four times greater risk of sudden death than nonsmokers. The risk appears to increase with increasing dosage as measured by the number of cigarettes smoked per day and diminishes with cessation of smoking.
9. The CHD mortality ratio for smokers compared with nonsmokers is greater for the younger age groups than for the older age groups. Although the smoker-to-nonsmoker mortality ratio narrows with increasing age, smokers continue to experience greater CHD death rates at all ages.
10. Cigarette smoking has been estimated to be responsible for up to 30 percent of all CHD deaths in the United States each year. During the period 1965 to 1980 there were over 3 million premature deaths from heart disease among Americans attributed to cigarette smoking. Unless smoking habits of the American population change, perhaps 10 percent of all persons now alive may die prematurely of heart disease attributable to

their smoking behavior. The total number of such premature deaths may exceed 24 million.

11. Cessation of smoking results in a substantial reduction in CHD death rates compared with those of persons who continue to smoke. Mortality from CHD declines rapidly after cessation. Approximately 10 years following cessation the CHD death rate for those ex-smokers who consumed less than a pack of cigarettes daily is virtually identical to that of lifelong nonsmokers. For ex-smokers who had smoked more than one pack per day, the residual risk of CHD mortality is proportional to the total lifetime exposure to cigarette smoke.
12. Epidemiologic evidence concerning reduced tar and nicotine or filter cigarettes and their effect on CHD rates is conflicting. No scientific evidence is available concerning the impact on CHD death rates of cigarettes with very low levels of tar and nicotine.
13. Smokers who have used only pipes or cigars do not appear to experience substantially greater CHD risks than nonsmokers.

Cerebrovascular Disease

1. Data from numerous prospective mortality studies have shown an association between cigarette smoking and cerebrovascular disease. This risk is most evident in the younger age groups, and the effect diminishes with increasing age, with little or no effect noted after age 65. No consistent dose–response effect has been demonstrated.
2. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage. However, the use of both cigarettes and oral contraceptives greatly increases the risk for subarachnoid hemorrhage among women.

Atherosclerotic Peripheral Vascular Disease and Aortic Aneurysm

1. Cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral arterial disease.
2. Smoking cessation plays an important role in the medical and surgical management of atherosclerotic peripheral vascular disease.
3. Death from rupture of an atherosclerotic abdominal aneurysm is more common in cigarette smokers than in nonsmokers.

Pharmacological and Toxicological Implications of Smoke Constituents on Cardiovascular Disease

1. Over 4,000 different compounds have been identified in tobacco smoke.

2. Nicotine exerts an effect on ganglionic cells, producing transient excitation. The pharmacological effects are small, but are reinforced several times daily in habitual smokers. The exact mechanisms whereby nicotine might influence cardiovascular events are unknown, but a lowering of the ventricular fibrillation threshold is dose related to nicotine levels.
3. Carbon monoxide may act to precipitate cardiac symptomatology or ischemic episodes in individuals already compromised by coronary disease. In addition, carbon monoxide binds to hemoproteins, potentially inhibiting their functions.
4. Several studies have shown that smokers may alter their smoking behavior when they switch to low-yield cigarettes. This compensatory behavior may lead to the increased uptake of gas phase constituents including carbon monoxide, hydrogen cyanide, and nitrous oxides.
5. It is unlikely that a "safe cigarette" can be developed that will reduce cardiovascular risk.

Changes in Cigarette Smoking Behavior in Clinical and Community Trials

1. Smokers involved in intervention programs demonstrate higher smoking cessation rates than those in control groups.
2. In general, the success of smoking intervention programs is related to the amount of intervention provided.

The Effect of Cigarette Smoking Cessation on Coronary Heart Disease

1. In the four intervention trials involving mortality followup of individual men for 5 to 10 years, the intervention groups had a combined total of 10 percent fewer CHD deaths than did the comparable control groups. Differences for other causes of death or for total deaths were not significant.
2. In these trials, the amount of cigarette smoking has been reduced 10 to 50 percent more in the intervention group than in the control group, demonstrating that intervention can alter smoking behavior.
3. In the two trials involving morbidity followup, the intervention groups had 4 and 45 percent lower total CHD incidence than did the respective control groups.
4. The relative reductions in CHD mortality in each of the four intervention studies involving individual followup are reasonably consistent with the reduction in CHD risk factors, and for a combination of all four studies, the reduction is statistically significant.

5. Numerous studies have shown that those who quit cigarette smoking experience a substantial decrease in CHD mortality and an improvement in life expectancy.
6. A number of prospective epidemiological studies indicate that former cigarette smokers substantially reduce their CHD and total death rates from that of current smokers.

Trends in Cardiovascular Diseases

The evidence supports the conclusion that changes in smoking habits have contributed to substantial improvement in mortality rates from the cardiovascular diseases in the United States.

Trends in U.S. Cigarette Use, 1965–1980

1. The proportion of current regular smokers declined steadily between 1965 and 1980. The decline was steeper among males (from 52.1 to 37.9 percent) than among females (from 34.2 to 29.8 percent).
2. The proportion of never smokers increased steadily from 1965 to 1980 among males (27.6 to 31.6 percent), except those 45 years old and older. Among females, only 20- to 34-year-olds showed an increase in proportion of never smokers.
3. The mean number of cigarettes smoked per day by current smokers increased slightly from 1970 to 1980 (from 20 to 21.7 cigarettes).
4. Males smoked a higher mean number of cigarettes throughout the 1970–1980 period, but the number for males and females increased about the same amount.
5. Heaviest daily consumption was in the middle-aged group (35–65 years). The greatest mean increase was observed among women aged 35 to 44.
6. The proportion of current smokers who smoked less than 20 cigarettes per day decreased between 1970 and 1980 (39.8 to 33.8 percent); the proportion smoking one pack exactly (20 cigarettes) remained constant (34.9 to 34.8 percent); the proportion smoking from 21 to 39 cigarettes increased slightly (13.7 to 14.5 percent); and the proportion smoking two or more packs per day increased from 11.4 to 16.8 percent.
7. The proportion of current smokers who attempted to quit three or more times decreased slightly from 1966 to 1980 (41.2 to 38.7 percent).
8. The proportion of former smokers having made three or more attempts to quit increased sharply (36 to 53.2 percent) from 1966 to 1975.
9. The proportion of current smokers who had attempted to quit during the past year increased from 1966 to 1980 (26.0 to 36.7 percent).

10. Among current smokers, younger persons and females were more likely than older persons and males to have attempted to quit during the previous 12 months.
11. The proportion of former smokers who had attempted to quit during the previous 12 months decreased from 1966 to 1975 (13.8 to 9.8 percent).
12. Among former smokers, younger persons and females were more likely than older persons and males to have quit during the previous 12 months.

SECTION 2. ARTERIOSCLEROSIS

Introduction and Definition of Terms

Arteriosclerosis is the predominant underlying cause of cardiovascular diseases, including coronary heart disease (CHD), cerebral infarction, arteriosclerotic peripheral vascular disease, and atherosclerotic aortic aneurysm. The specific relationships of tobacco use and these conditions, as well as an overview of known and suspected risk factors for cardiovascular disease, are reviewed in other sections.

Because arteriosclerosis is sometimes used in a broad sense to cover a variety of arterial lesions, the nomenclature and terminology used in this section will be defined.

Arteriosclerosis is a generic term that includes practically any arterial disease that leads to thickening and hardening of arteries of any size.

Atherosclerosis is a specific form of arteriosclerosis. Its most distinctive feature is the accumulation of lipid in the intima of large elastic arteries (aorta) and medium-sized muscular arteries (coronary, femoral, carotid, and others). In addition to lipid, cells, connective tissue fibers, and various blood components accumulate in the lesions. A number of complications, including thrombosis, hemorrhage into a plaque, and ulceration, can also occur in or upon the lesions. The hallmarks of atherosclerosis are its intimal location during the initial stage, the involvement of large- and medium-sized arteries, and the accumulation of fat in the lesion. Atherosclerosis is the form of arteriosclerosis that most frequently causes clinically significant disease.

Mönckeberg's medial calcific sclerosis, characterized by calcification of the medial layer of muscular arteries, and *arteriolosclerosis,* characterized by thickening, fibrosis, hyalinization, and narrowing of arterioles, are other types of arteriosclerosis quite distinct from atherosclerosis. They are beyond the scope of this section. Medial and arteriolar lesions have sometimes caused confusion in interpreting experimental studies, principally those in which rabbits and rats have been used. Only the intimal lesions that contain lipid and connective tissue elements in large elastic and medium-sized muscular arteries are models of human atherosclerosis.

The term *atheroma* has been used in several different ways, sometimes to refer to the entire process of atherosclerosis and sometimes to describe a specific lesion. Some pathologists use the word to mean a large atherosclerotic plaque containing a pool of necrotic cells, lipid, and connective tissue. Atheroma has also been used to refer to any lesion of atherosclerosis, including fatty streaks, fibrous plaques, or complicated or calcified lesions.

The following working definitions are offered for different types of atherosclerotic lesions detectable grossly after staining vessels with Sudan IV or other fat stains.

A *fatty streak* is a fatty intimal lesion that is stained distinctly by Sudan IV and shows no other underlying change. Fatty streaks are flat or only slightly elevated in opened fresh or immersion fixed vessels. They do not significantly narrow the lumina of blood vessels.

A *fibrous plaque* is a firm, elevated intimal lesion that in the fresh state is usually gray-white, glistening, and translucent. Human fibrous plaques characteristically contain fat. A thick fibrous connective tissue cap containing varying amounts of lipid covers a more concentrated "core" of lipid. If a lesion also contains hemorrhage, thrombosis, ulceration, or calcification, that lesion is classified according to one of the next two categories.

A *complicated lesion* is an intimal plaque in which there is hemorrhage, ulceration, or thrombosis with or without calcification.

A *calcified lesion* is an intimal plaque in which insoluble mineral salts of calcium are visible or palpable without overlying hemorrhage, ulceration, or thrombosis.

The term *raised atherosclerotic lesion* is sometimes used as a measure of atherosclerosis to include the sum of fibrous plaques, complicated lesions, and calcified lesions. Raised lesions are contrasted with fatty streaks, which typically show little or no elevation above the surrounding intimal surface.

Although this classification scheme implies a pathogenetic sequence, it can be used for descriptive purposes regardless of the theoretical pathogenetic interrelationships among the lesions.

Certain other intimal lesions are sometimes considered as subtypes of atherosclerosis or as lesions predisposing to atherosclerosis. These include musculoelastic or fibromuscular intimal thickening, gelatinous or edematous lesions, and organizing mural thrombi on an otherwise normal intima. The pathogenetic relationship of atherosclerosis and its clinical manifestations is less well established for these lesions, and quantitative information related to the natural history, topography, and geographic pathology is not available. "Rhythmic" or periodic wrinkling of the intimal surface of the aortas of children and adolescents is another change whose relationship to atherosclerosis has not been established.

Clinical Significance of Atherosclerosis

Atherosclerosis is the underlying cause of coronary heart disease (coronary occlusion, coronary thrombosis, myocardial infarction, and angina pectoris) and of one major type of stroke (cerebral thrombosis with infarction). Atherosclerosis also causes aortic aneurysms by weakening the aortic media via encroachment from primarily intimal lesions. Atherosclerosis also sets the stage for arteriosclerotic peripheral vascular disease by occlusive-thrombotic disease of the

distal aorta and by atherosclerotic lesions in the iliac-femoral vessels.

Previous Literature Reviews

The history of our knowledge about atherosclerosis was reviewed by Long (*39*). The morphology and pathogenesis of human atherosclerotic lesions were reviewed in detail by Duff and McMillan (*20*), and the gross and microscopic features of typical coronary and aortic human lesions at various ages were illustrated by McGill et al. (*44*). Data on the worldwide distribution of atherosclerotic lesions among different human populations were published in 1968 (*41*). Strong et al. (*72, 73*) reviewed the development of atherosclerosis by age, sex, and race, by the geographic variation in prevalence and extent of atherosclerosis, and by the relationship of atherosclerotic lesions to risk factors for coronary heart disease. A monograph on arterial smooth muscle cells by Geer and Haust (*22*) contains an extensive review of publications on the nature of cells in atherosclerotic lesions, descriptions of the histologic and ultrastructural features of arterial lesions, and electron micrographs illustrating atherosclerotic lesions. The published proceedings of international symposia on atherosclerosis (*25, 34, 63, 64, 65, 86*) contain review articles and reports of investigative work in atherosclerosis.

Natural History and Topography

Atherosclerosis begins in childhood, but does not usually become clinically manifest through its ischemic complications until later in life. The simple fatty streak is considered to represent the earliest lesion of atherosclerosis that can be easily recognized either grossly or histologically. The fatty streak is gradually converted into a fibrous plaque in which there is abundant connective tissue as well as lipid. These more advanced intimal lesions with increased amounts of mesenchymal tissue may enlarge to cause progressive stenosis of the vascular lumen. These lesions may undergo sufficient enlargement by accumulated lipid and connective tissue or superimposed mural thrombus to further narrow the lumen, or the lesions may become vascularized and undergo intramural hemorrhage or may become ulcerated and covered by thrombus. In these last instances, rapid occlusion of the artery may result. Under certain circumstances and in certain arterial segments, the lesion may so weaken the underlying media that an aneurysm is produced, or the lesion may become calcified—a change that may represent a healing process, but nevertheless reflects an advanced stage of the atherosclerotic process.

The strong association between cigarette smoking and the clinical manifestations of atherosclerosis is examined in other sections of this Report. This section examines the relationship between cigarette smoking and the development of atherosclerotic lesions and other stages of occlusive arterial disease.

A brief description of the topographic distribution of atherosclerosis in different arterial segments provides additional background information for this section. The topographic distribution of atherosclerotic lesions was reviewed by Duff and McMillan (*20*) and by Glagov and Ozoa (*23*). Schwartz and Mitchell (*68*) described selective involvement of some arteries and areas of localization of arterial plaques in their necropsy survey. Those studies were generally consistent, finding that lesions occur earliest and most extensively in the aorta. Pathologically demonstrable lesions usually develop later and less extensively in the coronary and cerebral arteries; the renal, mesenteric, and pulmonary arteries are the least susceptible to atherosclerotic lesions. A diagrammatic representation of the usual localization of arterial involvement by atherosclerosis is depicted in Figure 1, taken from the National Heart and Lung Institute (NHLI) task force report on arteriosclerosis (*79*).

Studies in the International Atherosclerosis Project (IAP) led to the following conclusions concerning atherosclerosis in the aorta and in the coronary, carotid, vertebral, and intracranial arteries (*43*). The severity of atherosclerosis in one artery does not predict the severity in another artery for an individual case. On a cross-cultural basis, however, the average predilection of a population to raised lesions in one artery is correlated with the predilection in other arteries. The rank order of location–race groups in the IAP is approximately the same regardless of whether the ranking is based on raised lesions in the coronary arteries, the thoracic aorta, the abdominal aorta, or the cerebral arteries. This finding is consistent with the hypothesis that environmental conditions predominantly determine the severity of atherosclerosis in a population, despite large differences in susceptibility to lesions among individuals or among different anatomic loci within the arteries of each person.

In general, the development of atherosclerosis follows a definite sequence. The aorta is involved first, beginning in infancy with fatty streaks that increase rapidly during puberty; fibrous plaques begin in the aorta in the third decade. Fatty streaks begin in the coronary arteries during puberty. They begin to increase significantly and become converted into fibrous plaques in the third decade of life in high risk populations. The carotid arteries begin to be involved with fatty streaks at approximately the same age as does the aorta. The other cerebral arteries begin to be involved at approximately the same age as do the coronary arteries. Raised lesions develop in the

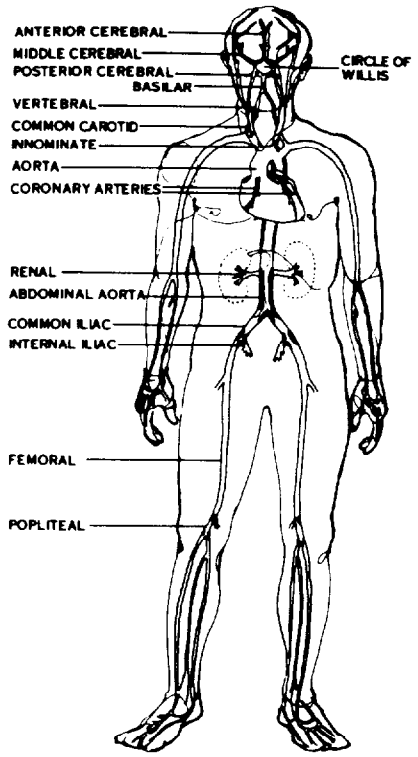


FIGURE 1.—Common sites of atherosclerotic lesions
SOURCE: U.S. Public Health Service (79).

carotid arteries at roughly the same age as in the aorta, but do not develop in the vertebral and intracranial arteries until much later.

Hypotheses of Atherogenesis

A succinct review of the major hypotheses concerning the atherosclerotic process (*47*) summarized various theories of atherogenesis with emphasis on the two major hypotheses—the lipid hypothesis, and the hypothesis that regards atherogenesis as a process involving the conversion of arterial mural thrombi into atherosclerotic plaques.

The lipid hypothesis is based on the frequent occurrence of excessive amounts of cholesterol and lipid in lesions, the positive association between elevated serum lipids and atherogenesis in man and in animals, the association of dietary saturated fats and cholesterol with atherogenesis in man and in experimental animals,

and the association between specific diseases and genetic disorders that affect lipid metabolism and atherogenesis.

The hypothesis concerning the conversion of mural thrombi into atherosclerotic plaques through tissue organization of the mural thrombi (the Duguid-Rokitansky concept) is based largely on pathological observations in man that show morphological evidence compatible with this view of atherogenesis. Such evidence is most convincing in relation to the middle or late development of plaques rather than to their early stages. Many investigators of atherosclerosis have accepted this theory as a basis for plaque progression or complication rather than as a theory of plaque initiation. The demonstration that platelets are capable of interacting with intimal smooth muscle cells to stimulate them to proliferate has now extended this theory to encompass the *initiation* of atherogenesis without necessarily invoking the classical sequence of thrombosis (*59*).

McMillan (*47*) pointed out that there has been a tendency for the proponents of one or the other of these theories to emphasize the rather exclusive importance of one hypothesis when considering various factors that are thought to be of particular importance for atherogenesis (such as cigarette smoking, hypertension, diabetes mellitus, or hyperlipoproteinemia). That is, the atherogenic factors often have been relegated to one or the other theory as independent factors that promote either lipid or thrombotic atherogenesis. Nevertheless, as McMillan (*47*) indicates, the two major theories are not mutually exclusive, but may complement one another in the initiation and progression of atherogenesis.

There is much support for the view that atherosclerosis is best accounted for by the known facts if it is regarded as a multifactorial disease and, in the words of McMillan, "polyetiologic and polypathogenetic."

The finding that some individual fibrous plaques are uniform for one or other of the sex-linked isoenzymes of 6-GPD (*12, 13, 14*) suggests that each mature plaque derives from a single cell and is the basis for a new theory of atherogenesis, the monoclonal hypothesis. This theory suggests that plaques may result from the transformation, genetic or otherwise, of individual cells of the vessel wall into a cell that will react to stimulation and form a plaque. Other observations that fatty streaks are not monotypic (*55*) and that thin plaques tend to be heterotypic, while thicker ones from the same aorta tend to be monotypic (*76*), suggest that the phenomenon of cell adaptation and selection rather than that of transformation may be the basis for plaque monotypism.

The arterial endothelium obviously has a key role in both the lipid and the thrombotic theories. In the lipid theory, the lipoprotein molecules traverse the endothelium in some fashion prior to being

accumulated in a plaque. The thrombotic theory also includes endothelial participation as an essential phenomenon. Endothelial damage or loss may be manifest either as increased permeability to macromolecules or as a focus for platelet adhesion, aggregation, and release; thus, these changes may be atherogenic stimuli. Exposure of the intima to lipoproteins and platelets may be mitogenic for smooth muscle cells, and can affect the arterial lesion by modulating the cellular production of collagen and glycosaminoglycans. This sequence of events indicates how the lipid and thrombotic theories can interrelate in early atherogenesis.

The most popular hypothesis to account for the accumulation of lipid in plaques involves the introduction of excessive amounts of plasma lipoproteins through the endothelial barrier to the intima. The lipoproteins, particularly low density lipoproteins (LDL), are internalized by smooth muscle and other connective tissue cells and are not metabolized rapidly; therefore, the lipid components accumulate in the cells. The sterols that are liberated in the cell lysosomes of arterial cells may become so excessive that high density lipoproteins (HDL) are unable to remove them from the cells and from the intima. With progressive cellular lipid accumulation, cellular necrosis may occur, causing lipid to be dispersed into the extracellular portions of the arterial wall. Thus, lipid may accumulate both intracellularly and extracellularly and may act as a local cause of injury.

When weighing the evidence linking tobacco usage with the development of atherosclerotic lesions, one should consider these theories of atherogenesis as well as the natural history of atherosclerosis presented earlier in order to make judgments about possible mechanisms and the stages at which the process might be affected.

Epidemiological Evidence Linking Cigarette Smoking With Atherosclerosis

Cigarette smoking is a major risk factor for coronary heart disease, peripheral vascular disease, and other clinically significant sequelae of atherosclerosis. A key question is whether cigarette smoking has an effect on the development of the arterial lesions, the terminal occlusive events, or both. Until the recent past, few investigators specifically designed studies to answer questions dealing with the association between cigarette smoking habits and the development of atherosclerotic lesions in the aorta and coronary arteries.

In the 1971 Report of the Surgeon General *The Health Consequences of Smoking* (*80*), reports of such studies were reviewed and summarized. Since that time, a number of additional reports have been published dealing with the relationship between cigarette smoking and atherosclerosis of the coronary arteries, aorta and

peripheral arteries, arterioles within the myocardium, and cerebral vessels. The evidence relating cigarette smoking and autopsy evidence of atherosclerotic disease in each of these areas is reviewed separately and summarized in individual tables in this section.

Coronary Arteries

Table 1 summarizes the studies that have examined the relationship between cigarette smoking and autopsy evidence of atherosclerosis in the coronary arteries. Auerbach et al. (*6*) found more coronary atherosclerosis in smokers than in nonsmokers and a concomitant increase in the amount of atherosclerosis with the amount of cigarette smoking. An interim report by Strong et al. (*75*) concluded that atherosclerotic involvement of aortas and coronary arteries was greatest in heavy smokers and least in nonsmokers among autopsied men in New Orleans. A report by Viel et al. (*81*) on accidental deaths in Chile stated that there was no relationship between atherosclerotic lesions and the use of tobacco; however, examination of the data indicated that heavy smokers in the 50- to 54-year and 55- to 59-year age groups exhibited higher percentages of the left anterior descending coronary intima involved by atherosclerotic lesions than did nonsmokers. Apparently these differences were not statistically significant.

A detailed study of smoking and atherosclerosis in deceased men in New Orleans has been conducted. Several reports based on the findings of that study, as well as various interpretations of those findings, have been published. Strong and Richards (*74*) reported the basic findings on the association of cigarette smoking and atherosclerosis in 1,320 autopsied men in New Orleans, 25 to 64 years of age. Coronary lesions were evaluated visually in coded specimens and objectively by analysis of post mortem radiographs. Using schedules that had been tested on pairs of living persons (*45*), interviewers obtained estimates of cigarette smoking habits of the deceased men from surviving relatives. Data were compared for black men and white men and also were analyzed in groups according to the presence or absence of diseases thought to be associated with smoking or with coronary heart disease (emphysema, lung cancer, myocardial infarction, hypertension, diabetes mellitus, stroke, etc.). Atherosclerotic involvement of the coronary arteries was greatest in heavy smokers and least in nonsmokers for both races in the total sample and in the basal group (those cases least influenced by the bias of autopsy selection). The data for these groups are presented in Table 1.

The study by Strong and Richards (*74*) included approximately the same number of autopsied subjects from New Orleans as had the previously reviewed study by Auerbach et al. (*6*) in East Orange, New Jersey. Even though the methods of evaluation of arterial

TABLE 1.—Autopsy studies of atherosclerosis involving the coronary arteries

Study	Population	Data collection method	Measure of atherosclerosis	Results				
				Smoking	No atherosclerosis	Slight	Moderate	Advanced
Auerbach et al. (6)	1,372 autopsies of men who did not die of CHD	Interview with relatives	Visual protocol	None	5.6	57.3	21.8	15.3
				<20	2.6	30.9	37.3	29.2
				20–34	.8	19.7	42.1	37.4
				40+	.6	18.1	35.4	45.9
Avtandilov (8)	259 males and 141 female autopsies	Not specified	Not specified	Comparative size of mean area of atherosclerotic lesions in inner coat of coronary arteries				
					Right coronary artery		Left coronary artery	
					Smoker	Nonsmoker	Smoker	Nonsmokers
				30–39	15.5 (30)[1]	1.3 (32)	6.3[1]	2.2
				40–49	23.6 (34)	11.5 (27)	15.8[1]	4.4
				50–59	36.3 (39)[1]	14.8 (39)	27.9[1]	9.9
				60–69	31.9 (32)[1]	23.8 (36)	26.5[1]	22.5
				70–79	41.9 (18)	31.7 (36)	26.1	35.8
				NOTE: The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.				
Viel et al. (81)	1,150 males and 290 females autopsied following violent death	Interview with relatives	Not specified	Graphic data presentation only, but no association noted				

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Strong et al. (75)	747 New Orleans males 20–64 years of age at death	Interviews with next of kin within 8 weeks of death	IAP protocol, visual grading, and optical scanning	
Strong and Richards (74)	1,320 autopsies of males aged 25–64	Interview with next of kin	Visual grading and optical scanning	Mean percent of coronary artery intimal surface involved with raised lesions for total sample, males

	Average number cigarettes smoked per day		
Age	0	1–24	25+
		White males	
25–34	3	8	10
35–44	21	27	26
45–54	32	37	39
55–64	36	45	47
		Black males	
25–34	4	4	12
35–44	12	16	23
45–54	19	31	35
55–64	32	31	33

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Auerbach et al. (4)	1,056 autopsies of male veterans	Interview with relatives	Visual and microscopic evaluation	Distribution (in percentages) of degrees of fibrous thickening, of atheroma, and of calcification by smoking habits standardized for age (microscopic coronary study)

Degree of findings	Never smoked regularly	Current cigarette smokers: <pack per day	1–2 packs per day	2+ packs per day	Cigar/ pipe	Ex-cigarette smokers
Fibrous thickening						
None	50.1	3.9	0.6	0.4	4.5	5.0
Slight	20.1	26.5	8.0	5.1	24.4	30.6
Moderate	29.0	59.1	72.6	72.3	54.8	57.4
Advanced	0.8	10.5	18.8	22.2	16.3	7.0
Atheroma						
None	82.5	74.5	69.9	66.1	68.2	72.8
Slight	4.1	4.0	3.7	3.1	4.5	3.9
Moderate	13.1	19.2	20.6	20.8	23.4	21.5
Advanced	0.3	2.3	5.8	10.0	3.9	1.8
Calcification						
None	85.8	81.5	78.1	73.5	75.5	79.2
Slight	4.5	4.1	3.8	4.3	6.2	4.3
Moderate	8.4	10.3	11.1	11.2	13.4	12.7
Advanced	1.3	4.1	7.0	11.0	4.9	3.8

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results

Distribution by percentage of degree of atherosclerosis by smoking habits standardized for age (macroscopic study)

Degree of atherosclerosis	Never smoked regularly	Current cigarette smokers: < pack per day	1-2 packs per day	2+ packs per day	Cigar/ pipe	Ex-cigarette smoker
None or minimal	59.8	45.2	36.6	32.6	36.3	50.9
Slight	24.7	26.9	27.9	27.5	28.4	25.5
Moderate	10.2	16.2	16.0	16.5	21.0	12.6
Advanced	5.3	11.7	19.5	23.4	14.3	11.0
Total	100.0	100.0	100.0	100.0	100.0	100.0

Study	Population	Data collection method	Measure of atherosclerosis
Lifšic (37)	894 autopsies of males 20–79 at death in Yalta	Interview with relatives	Visual grading

Ratio of the extent of atherosclerotic lesions in the average coronary artery between nonsmokers and smokers

	Total athero-sclerosis	Fatty streak	Fibrous plaque	Compli-cated lesion	Calcified lesion	Raised lesion
Nonsmoker to heavy smoker	1.0	1.1	1.0	1.5	0.6	1.0
Nonsmoker to smoker	1.0	1.1	1.1	1.0	0.6	1.0

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Schettler et al. (63)	Autopsies of 89 males aged 60–94 at death in Tokyo	Interview with relatives	Visual grading	Stenosis

Smoking	No	Yes	Total
No	6	8	14
Yes, daily	8	67	75
Total	14	75	89

Study	Population	Data collection method	Measure of atherosclerosis	Results
Rhoads et al. (56)	109 autopsies of Japanese American males born 1900–1919 who participated in Honolulu heart study	Interview with subject	AHA panel	Mean coronary atherosclerosis grade versus selected attributes

Examination variables	Regression coefficients: Simple	Regression coefficients: Multiple[1]
Relative weight (%)	0.031[3]	0.025[2]
Cigarettes/day	0.022[2]	0.024[3]
Cholesterol(mg/dl)	0.011[3]	0.009[3]
Triglycerides(mg/dl)	0.002[2]	NS[4]
Glucose(mg/dl)	0.004[2]	NS[4]
Hematocrit (%)	0.069[2]	NS[4]

[1] Multiple regression was done by a step-wise elimination procedure beginning with the set of variables shown; coefficients are for the final step. Multiple correlation (final step) = 0.46 (N = 108).
[2] Significant at 0.05 level.
[3] Significant at 0.01 level.
[4] NS, variable included in first step; deleted as not significant at 0.05 level.

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Tracy et al. (77)	Autopsies of 1,320 white and black males, age 25–64 at death	Interview with next of kin	Visual grading	

Means of observed minus expected raised-among-lesions(O–E), fatty streaks among flat surfaces (FaF), all types lesion (ATL), and number of cases (N) by age, race, and cause of death according to smoking category[1]
Coronary arteries combined.

	O-E			FaF			ATL			N		
Age (yr)	0	1–24	25+	0	1–24	25+	0	1–24	25+	0	1—24	25+
White basal												
25–34	5.9	5.1	18.3	4.4	9.3	5.9	7.3	15.7	13.4	12	25	14
35–44	-2.2	13.4	11.8	13.9	7.3	16.9	24.9	21.1	38.1	20	22	25
45–54	4.5	0.2	11.7	16.4	18.7	14.5	30.6	37.0	36.9	10	28	41
55–64	2.8	3.4	5.8	17.1	17.3	19.5	40.5	49.0	49.8	21	19	32
White CHD												
25–34	X	X	X	X	X	X	X	X	X	0	0	1
35–44	17.9	8.5	16.0	16.9	29.1	20.4	37.3	69.6	60.9	6	9	15
45–54	0.8	7.5	6.3	23.2	23.9	25.7	68.8	64.9	70.0	5	24	33
55–64	3.9	5.4	30.0	24.5	15.7	66.7	70.7	64.7	9	21	32	
Black basal												
25–34	-3.9	-2.6	3.6	8.4	9.0	12.7	11.4	11.3	19.6	24	76	18
35–44	-7.4	-8.2	-9.4	11.2	17.3	19.6	13.8	25.5	30.6	15	70	31
45–54	-14.9	-15.5	-3.7	19.4	20.6	21.7	28.0	32.0	37.5	19	51	26
55–64	-19.6	-2.8	-1.1	28.1	19.9	21.9	41.9	39.5	33.8	27	41	15
Black CHD												
25–34	X	-9.7	X	X	17.3	X	X	27.8	X	0	5	0

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results										
			35–44	X	4.4	–0.4	X	32.2	32.1	X	60.3	62.1	2	8	12
			45–54	X	5.5	0.4	X	25.7	31.4	X	65.7	70.4	2	25	12
			55–64	–0.1	–4.7	7.2	31.4	31.1	20.8	80.3	57.4	62.4	11	15	9
			[1] ATL as percent surface fatty streaks (F) plus raised lesions (R); FaF = F + (100 – R);0–E in percentage units explained in the text; X indicates subgroups having fewer than five members.											
Holme et al. (*29*)	129 autopsies from 16,2000 males aged 40–49 in Oslo prospective CHD study	Interview with subject	Visual grading	Correlation coefficient between number of cigarettes and raised lesions in the coronary arteries = .039, not significant.										
Sternby (*71*)	60 autopsies of 703 males in CHD study in Malmo, Sweden	Interview with subject	Visual grading	Smoking and stenosis or atherosclerosis in the left anterior descending coronary artery										
				Smoking category		Number		LAD raised lesions			Coronary artery stenosis			
				Non		3		68			33			
				Ex		8		52			38			
				Light		18		45			39			
				Heavy		17		54			59			

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results
Sorlie et al. (*70*)	139 autopsies of 9,824 Puerto Rican males aged 35–79 in a prospective study	Interview with subject	Visual grading	Association of atherosclerosis in coronary arteries with antemortem characteristics: simple correlation coefficients (Puerto Rico heart health program)

	Correlation coefficients		
Characteristics measured at exam 1	Total (139)	Rural (36)	Urban (103)
Systolic blood pressure	0.22	0.07	0.30
Diastolic blood pressure	0.26	0.09	0.30
Serum cholesterol	0.42	0.59	0.38
Age, exam 1	0.01	0.32	–0.08
Relative weight	0.21	–0.15	0.25
Physical activity	–0.18	0.06	–0.22
Blood glucose	0.20	–0.04	0.21
Hematocrit	0.14	0.38	0.12
Education level	0.14	–0.40	0.24
Income	0.16	–0.17	0.18
Cigarettes smoked	–0.16	–0.05	–0.22
Calories (24-hour recall)	–0.14	–0.43	–0.07
Starch (24-hour recall)	–0.17	–0.29	–0.09
Alcohol (24-hour recall)	–0.10	–0.10	–0.13
Total fats (24-hour recall)	–0.04	–0.53	0.03
Triglycerides (fasting)	0.23	0.49	0.19
Ventricular rate	0.13	0.20	0.08
Vital capacity	–0.19	–0.13	–0.16

lesions were not identical, the findings from both of these large studies of autopsied men in the United States were remarkably similar. Both studies reported more extensive coronary atherosclerosis among the cigarette smokers than among the nonsmokers, and for the major comparisons, with only rare exceptions, there was an orderly progression of least extensive lesions in nonsmokers, intermediate extent of lesions in light or moderate smokers, and most extensive lesions in heavy smokers.

In the New Orleans study (*74*), lesions were measured not only by visual evaluation, but also by optical electronic scanning of radiographic images of the flattened arteries. The measurements of lesions from radiographs—relative mean coronary wall thickness and percentage of the coronary artery intima involved with calcification—were consistently greater for the heavy smokers than for the nonsmokers. A variety of statistical analyses on smoking measures and atherosclerotic lesions were performed to determine the significance of the various differences and trends. These analyses confirmed that the major differences between the heavy smokers and the nonsmokers in extent of raised atherosclerotic lesions (the sum of fibrous plaques, complicated lesions, and calcified lesions) were significant. A one-way multivariate analysis of nine atherosclerotic variables clearly indicated that there were statistically significant differences among the three categories of smokers (heavy, light to moderate, and nonsmokers) for mean coronary wall thickness, raised lesions in the coronary arteries, percentage of cases positive for fibrous plaques, percentage of cases positive for complicated lesions, and percentage of cases positive for calcified lesions, with lower values in nonsmokers and higher values in the heavy smokers.

Patel et al. (*53*) evaluated this same data on smoking and atherosclerotic lesions to examine further the interrelationships with measures of obesity. The confounding effects of diseases such as hypertension and diabetes mellitus were controlled by excluding such cases from the analysis. The confounding effects of age and measures of smoking habits on the association between atherosclerosis and obesity were controlled by multivariate regression analysis. This analysis disclosed an inverse relationship between smoking habits and obesity. There was also a weak positive association—when age and smoking were controlled for—between measures of obesity and mean coronary wall thickness and raised lesions in the coronary arteries among whites, but not among blacks. In the black men, again with age and smoking controlled in the analysis, a weak association between fatty streaks in the coronary arteries and obesity was found. This analysis confirmed the previously reported relationships between smoking habits and atherosclerosis, as measured by mean coronary wall thickness, coronary calcifications, and raised lesions in the coronary arteries.

Since their first report in 1965, Auerbach and his associates have investigated the relationship of cigarette smoking to microscopic findings in the coronary arteries (*4*). This study indicated that lesions were most extensive in cigarette smokers and confirmed earlier studies by Auerbach et al. (*6*) and Strong and Richards (*74*). The microscopic portion of the Auerbach et al. study (*4*) showed that fibrous thickening, atheroma, and calcifications of the coronary arteries all increased with increasing number of cigarettes smoked per day. They also found that the fibrous thickening of arteries increased in relation to the number of cigarettes smoked per day as the size of the artery decreased; i.e., it was least in the coronary arteries and greatest in the myocardial arteries.

Lifšic (*37*) reported on the relationship of cigarette smoking to coronary atherosclerotic lesions based on the Yalta sample from the World Health Organization (*87*) autopsy study of five cities in Europe. Information on cigarette smoking was obtained by means of interviews with the subjects' near relatives. The prevalence and extent of atherosclerotic lesions were evaluated in autopsies of 865 men, aged 20 to 79 years, out of the 1,220 deaths occurring in Yalta residents of this age and sex group during the period of study. There was a positive association of smoking with the extent of coronary calcification; however, the author explained this association as being related to coexisting alcohol consumption and stated that smoking alone tended to be negatively associated with coronary calcification. The following paragraph from Lifšic's discussion provides additional information from this report.

> There was little significant difference between smokers and nonsmokers in the prevalence and extent of atherosclerotic lesions in the coronary arteries. Thus, of the total of 210 comparisons of different indices of the prevalence and extent of atherosclerotic lesions between subgroups X and W, significant differences positively correlated with smoking were found in only 20. The tendency toward a positive correlation of coronary atherosclerosis with smoking was found mainly in subjects up to the age of 50, but after 60 the opposite tendency prevailed. These age peculiarities agreed with data from other studies showing that differences in the degree of atherosclerosis between smokers and nonsmokers . . . are more distinct below age 60.

The author also mentioned a positive association between smoking and coronary calcification in "strenuous workers." A note added in proof to Lifšic's article states, "Additional study of this material by individually matched case–control analyses revealed a marked trend toward a positive association between smoking and atherosclerotic raised lesions in the coronary arteries" (*82*). Thus, while the author's abstract does not indicate an important relationship of smoking and coronary atherosclerosis, there are findings in the study that do

indicate significant relationships between smoking and coronary atherosclerosis, especially in the younger subjects.

A subsequent study by Vikhert et al. (*83*) on material from five cities in the U.S.S.R. evaluated the effect of nutritional status and tobacco smoking on atherosclerotic changes in the coronary arteries as measured by a visual planimetric method. This material was also utilized for a WHO-sponsored epidemiological study of atherosclerosis (*87*). The vessels examined were from 430 men 40 to 69 years of age. The major analyses concerning tobacco smoking were made from 313 male heavy smokers and 82 nonsmokers. The investigators studied both manual workers and white-collar workers and found that tobacco smoking in combination with overnourishment had a much more positive effect on the development of coronary atherosclerosis in white-collar workers than in the manual workers.

Prospective epidemiologic studies of cardiovascular disease with autopsy followup provide additional information concerning the relationship of smoking to atherosclerotic lesions in the artery wall. The epidemiological studies in Oslo, Puerto Rico, and Honolulu are characterized by careful documentation of selected major risk factors, including cigarette smoking habits during life, and by standardized evaluation of atherosclerotic lesions at autopsy (*29, 56, 70*). Each of these three studies reported findings on the relationship of CHD risk factors to atherosclerotic lesions in more than 100 autopsies of deceased men who had been part of larger cohorts that had been examined and followed during life. In addition, a smaller study from Malmö, Sweden, had some of the same features as these larger studies (*71*). The Oslo, Malmö, and Puerto Rico studies used identical methods for grading the extent of atherosclerotic lesions. These prospective epidemiologic studies with autopsy followup are in general agreement concerning the relationship of serum cholesterol levels and blood pressure to the extent of atherosclerotic lesions in the coronary vasculature. The findings concerning the relationship of cigarette smoking to the extent of coronary atherosclerosis are not uniform. The Honolulu study (*56*) showed a significant relationship between smoking habits and extent of coronary atherosclerosis. The Oslo study (*29*) did not show a significant relationship between cigarette smoking and coronary atherosclerosis. The Puerto Rico study (*70*) also did not show a significant relationship between smoking and the extent of coronary atherosclerosis. A somewhat similar study from Japan by Hatano and Matsuzaki (*26*) indicated a significant relationship between cigarette smoking and coronary artery stenosis. Thus, there is some inconsistency concerning the association between cigarette smoking habits and coronary atherosclerosis in the prospective epidemiologic studies with autopsy followup.

In considering this entire body of evidence, however, the preponderance of evidence suggests that cigarette smoking has an effect on the development of atherosclerotic lesions in the coronary artery wall in the U.S. population, and that its effect is not limited to those events immediately surrounding the occlusive episode.

Small Arteries in the Myocardium

Table 2 reviews those studies that have examined the relationship between cigarette smoking and lesions of the arterioles within the myocardium. Auerbach et al. (*7*) found a relationship between smoking habits and thickening of the walls of the arterioles and small arteries of the myocardium. Auerbach et al. (*4*) also performed a microscopic study of coronary artery lesions in autopsied men in relation to previous smoking histories. In the microscopic portion of this study, fibrous thickening, atheroma, and calcification increased with an increased number of cigarettes smoked per day. Moderate to advanced hyaline thickening of the arterioles in the myocardium was strongly related to smoking. It was found in 98.6 percent of the autopsied subjects with a two pack per day smoking habit and not found in the group of subjects who never smoked regularly. Naeye and Truong (*51*) reported essentially similar alterations in the intramyocardial arteries, which developed more rapidly in cigarette smokers than in nonsmokers.

The Aorta

Those studies that provide autopsy and other evidence for the relationship between cigarette smoking and atherosclerosis of the aorta are summarized in Table 3.

Wilens and Plair (*85*) found significantly more severe sclerosis of the aorta in cigarette smokers than in nonsmokers. Sackett and Winkelstein (*61*) reported that elderly cigarette smokers had significantly higher rates of aortic calcification, detected on chest X-ray, than did nonsmokers. Sackett et al. (*60*), in an autopsy study, found a significant relationship between the use of cigarettes and the severity of aortic atherosclerosis. An interim report by Strong et al. (*75*) concluded that atherosclerotic involvement of aortas was greatest in heavy smokers and least in nonsmokers among autopsied men in New Orleans.

Most of these studies, reviewed in the 1971 Report of the Surgeon General *The Health Consequences of Smoking* (*80*), indicate that differences between heavy cigarette smokers and nonsmokers are particularly great in young individuals, and that heavy smokers have increased surface involvement with fibrous plaques or more advanced atherosclerotic lesions.

Since the 1971 review, a study of smoking and atherosclerosis in deceased men in New Orleans has been completed. Several reports

TABLE 2.—Autopsy studies of atherosclerosis involving small arteries in the myocardium

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Auerbach et al. (7)	1,184 males autopsied at VA	Records and family	Biopsy of myocardium	Grade of thickness of walls of arterioles[1]

Age	Smoking	Number of men: Total	Grade 0	Grade 1	Grade 2, 3	Percentage of men: Total	Grade 0	Grade 1	Grade 2, 3
<45	None	22	2	19	1	100.0	9.1	86.4	4.5
	Cigar-pipe	4	—	1	3	100.0	—	25.0[2]	75.0[2]
	Ctte[3] 1-19	50	1	31	18	100.0	2.0	62.0	36.0
	Ctte 20-39	85	4	35	46	100.0	4.7	41.2	54.1
	Ctte 40+	29	—	10	19	100.0	—	34.5	65.5
45-59	None	15	1	12	2	100.0	6.7	80.0	13.3
	Cigar-pipe	13	—	8	5	100.0	—	61.5	38.5
	Ctte 1-19	33	—	17	16	100.0	—	51.5	48.5
	Ctte 20-39	99	—	35	64	100.0	—	35.4	64.6
	Ctte 40+	50	—	11	39	100.0	—	22.0	78.0
60-69	None	56	4	36	16	100.0	7.1	64.3	28.6
	Cigar-pipe	35	—	22	13	100.0	—	62.9	37.1
	Ctte 1-19	92	—	44	48	100.0	—	47.8	52.2
	Ctte 20-39	193	—	58	135	100.0	—	30.1	69.9
	Ctte 40+	87	—	21	66	100.0	—	24.1	75.9
70+	None	32	2	18	12	100.0	6.3	56.2	37.5
	Cigar-pipe	40	—	19	21	100.0	—	47.5	52.5
	Ctte 1-19	30	—	12	18	100.0	—	40.0	60.0
	Ctte 20-39	46	—	12	34	100.0	—	26.1	73.9
	Ctte 40+	9	—	3	6	100.0	—	33.3[2]	66.7[2]

[1] In the right ventricular wall of 1,020 men by age and smoking habits.
[2] Percentages based on less than 10 cases.
[3] Ctte indicates cigarettes.

TABLE 2.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Auerbach et al. (4)	1,056 males autopsied at VA	Relatives and records	Microscopic examination	Distribution by percentage of degree of fibrous thickening of myocardial arteries, subepicardial arteries, and hyaline thickening of myocardial arterioles (microscopic myocardial study), by smoking habit standardized by age

Degree of findings	Never smoked regularly	Current cigarette smokers: <1 pack per day	Current cigarette smokers: 1–2 packs per day	Current cigarette smokers: 2+packs per day	Cigar/pipe	Ex-cigarette smokers
Myocardial arteries						
None or minimal	97.3	24.1	2.9	1.1	22.0	32.0
slight	2.7	62.2	37.1	29.6	70.6	63.2
Moderate	+16	12.3	39.0	45.0	6.7	4.2
Advanced	—	1.4	21.0	24.3	0.7	0.6
Total	100.0	100.0	100.0	100.0	100.0	100.0
Subepicardial arteries						
None or minimal	74.7	17.5	2.4	1.4	21.5	26.2
Slight	24.9	56.8	35.1	32.7	64.8	60.5
Moderate	0.4	19.0	28.8	23.8	9.9	11.6
Advanced	—	6.7	33.7	42.1	3.8	1.7
Total	100.0	100.0	100.0	100.0	100.0	100.0
Myocardial arterioles						
None or minimal	92.0	2.1	—	—	—	3.2
Slight	8.0	28.7	2.2	1.4	39.6	40.8
Moderate	—	20.8	9.6	7.9	19.6	19.1
Advanced	—	48.4	88.2	90.7	40.8	36.9
Total	100.0	100.0	100.0	100.0	100.0	100.0

TABLE 3.—Autopsy studies of atherosclerosis involving the aorta

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Wilens and Plair (*85*)	989 consecutive necropses at NY VA hospital	Patient chart	Visual grading	Percent of subjects by smoking status and atherosclerosis

Severity of sclerosis	Non-smoker	Heavy	Moderate	Light	Pipe/ cigar	Other
Number	161	199	288	152	70	119
Percent above average	9.9	25.1	26.4	19.1	10	10.9
Percent average	60.2	61.3	62.5	63.2	60	63.0
Percent below average	29.8	13.6	11.1	17.8	30	26.1

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Strong and Richards (*74*)	1,320 autopsies of males aged 25–64 at death	Interview with relatives	Visual grading	Mean percent of intimal surface of abdominal aorta involved with raised lesions

	Average number of cigarettes smoked per day		
Age and race	0	1–24	25+
White males			
25–34	1	7	7
35–44	14	33	44
45–54	33	52	56
55–64	46	63	71
Black males			
25–34	4	7	9
35–44	6	20	28
45–54	14	37	45
55–64	26	51	56

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Sackett and Winkelstein (*61*)	590 white male admissions to Roswell Park Memorial Institute in 1955	Patient questionnaire	Chest X-ray for calcification in thoracic aorta	The relationship between smoking and calcification of the thoracic aorta

	Nonsmokers		Smokers			
Age group	Number	Percent with calcification	Number	Percent with calcification	Probability value[1]	Totals
50–59	61	13	131	11	0.4	192
60–69	90	18	124	26	0.2	214
70 and over	116	37	63	54	0.02	184
Totals	267	25	323	26	—	590
Age-adjusted percent	—	22	—	30	—	—

[1] Chi-square of independence, two-tailed.

The relationship between amount smoked and calcification of the thoracic aorta

	Nonsmokers		Light smokers		Heavy smokers		
Age group	Number	Percent with calcification	Number	Percent with calcification	Number	Percent with calcification	Totals
50–59	61	13	104	9	27	22	192
60–69	90	18	107	24	17	35	214
70 and over	116	37	63	56	5	40	184
Totals	267	26	274	29	49	27	590
Age-adjusted percent	—	22	—	29	—	32	—

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Sackett et al. (*60*)	1,019 consecutive autopsies of white patients	Standardized interview with patient on admission	Visual grading on a numerical scale	Mean age-adjusted atherosclerosis ridits versus graded use of cigarettes and alcohol

	Alcohol	Cigarettes	
Oz/day	None	½ pack	½ pack+
None	.351	.468	.498
0.5–1.5	.424	.570	.568
1.6+	.428	.528	.589

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Strong et al. (*75*)	Autopsies of 741 males 20–64 years at death	Interview with relatives	Visual grading and optical scanning	Mean percentage of intimal surface of aorta involved with raised lesions by age, race, and average rate of cigarette smoking in the last 10 years of life

	Cigarettes per day		
Age and race	0	1-24	25+
White males			
35–44	16	35	49
45–54	29	52	54
55–64	48	66	70
Black males			
35–44	3	22	24
45–54	12	38	50
55–64	21	50	49

TABLE 3 —Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Lifšic (37)	865 autopsies of males aged 20–79 at death in Yalta	Relatives and records	Visual grading	Prevalence of atherosclerotic lesions in the abdominal aorta in different subgroups (percentage)

Smoking group	Fatty streak	Fibrous plaque	Complicated lesion	Calcified lesion
Never	96.5	96.0	43.0	25.0
Light	92.8	96.5	53.4	42.3
Heavy	90.7	97.5	60.9	57.3

Extent of atherosclerotic lesions (percentage of surface) in the abdominal aorta

Smoking group	Fatty streak	Fibrous plaque	Complicated lesion	Calcified lesion
Never	7.0	28.1	2.0	1.2
Light	6.1	31.8	5.1	2.2
Heavy	5.8	29.5	4.1	3.4

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Rhoads et al. (56)	124 Japanese American males autopsied as part of the Honolulu heart study	Interview with subject	Visual by AHA panel method	Correlation coefficients among selected autopsy and examination variables[1]

	Aorta (N = 124), atherosclerosis grade
Age at death	0.30[3]
Examination variables	
Height (cm)	-0.12
Relative wt. (%)	-0.10
Cigarettes/day	0.14
Cholesterol (mg/dl)	0.24[3]
Triglycerides (mg/dl)	0.14
Uric acid (mg/dl)	-0.05[2]
Glucose (mg/dl)	0.15
Hematocrit (%)	-0.03
Vital capacity (liters)	-0.23[3]
Alcohol (gm)	-0.08[2]
Systolic pressure (mm Hg)	0.29[3]
Diastolic pressure (mm Hg)	0.05
Mean coronary grade	0.50[3] (96)[4]
Aorta grade	

[1] N = number of specimens.
[2] Significant at 0.05 level.
[3] Significant at 0.01 level.
[4] When a correlation coefficient is based on less than 95 percent of the specimens available (because of missing data), the number of observations is indicated in parentheses. There were 96 autopsies with both aorta and coronary vessel grades available, 13 with coronary only, and 28 with aorta only.

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Auerbach and Garfinkel (5)	1,412 males autopsied at VA hospital	Family	Visual grading	Percentage of selected findings by smoking habits

Percentage of cases[1]

Findings	Never smoked regularly	"Current" cigarette smokers: 1 pack per day	1-2 packs per day	2+ packs per day	Cigar or pipe	Ex-cigarette smoker
Thoracic aorta						
Many or diffuse distribution of plaques	16	26	41	37	27	29
Moderate or advanced ulceration	4	6	14	12	10	8
Moderate or advanced calcification	56	63	74	74	53	67
Thrombus present	4	7	14	11	11	9
Abdominal aorta						
Many or diffuse distribution of plaques	28	54	68	79	46	53
Moderate or advanced ulceration	7	19	27	27	13	22
Moderate or advanced calcification	63	76	84	88	74	81
Thrombus present	7	23	23	31	14	23

[1] Percentages are adjusted to distribution by age group of all men in study.

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Sternby (71)	60 autopsies from 703 males enrolled in a CHD study in Malmo, Sweden	Interview with subject	Visual grading	Smoking and atherosclerosis of the aorta

Smoking category	Number	Raised lesions in the abdominal aorta
Non	3	26
Ex	8	43
Light	18	53
Heavy	7	83

Smoking and atherosclerosis in peripheral arteries

		Iliac artery	Femoral artery		Lower leg artery	
Smoking category	N	Raised lesions	Raised lesions	Sterosis (%)	Raised lesions	Stenosis (%)
Non	3	17	20	0	2	0
Ex	8	18	43	33	18	22
Light	18	29	23	6	3	11
Heavy	17	50	50	35	12	47

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Tracy et al. (77)	Autopsies of 1,380 white and black males aged 25–64 at death	Interview with relatives	Visual exam	Means of observed minus expected raised-among-lesions (O–E), fatty streaks among flat surfaces (FaF), all types of lesions (ATL), and number of cases (N) by age, race, and cause of death according to smoking category[1], abdominal aorta

	O–E			Faf			ATL		
Age	0	1–24	25+	0	1–24	25+	0	1–24	25+
White basal									
25–34	-3.7	3.9	0.6	25.3	32.1	36.6	26.4	36.6	34.7
35–44	-7.3	5.0	12.7	22.8	30.8	35.5	27.9	48.1	64.7
45–54	7.7	6.1	3.6	21.3	28.9	31.4	47.3	57.3	65.8
55–64	-0.6	3.0	6.7	33.7	33.1	35.5	56.5	68.6	76.2
White CHD									
25–34	X	X	X	X	X	X	X	X	X
35–44	-18.7	15.3	6.8	43.2	28.2	39.2	55.3	67.9	68.0
45–54	8.0	3.6	7.3	25.7	40.8	33.1	50.0	81.4	73.4
55–64	4.5	5.4	2.2	44.3	37.7	40.1	77.7	82.8	83.7
Black basal									
25–34	-5.3	-3.5	-3.8	28.6	32.8	36.8	30.7	34.9	38.6
35–44	-16.9	-3.1	-3.9	26.5	31.8	33.0	27.8	43.9	45.6
45–54	-15.7	-7.3	-5.4	25.0	32.7	37.4	33.8	47.2	60.0
55–64	-9.5	-0.3	-2.8	29.7	31.6	32.1	43.9	61.6	55.5
Black CHD									
24–34	X	6.3	X	X	39.7	X	X	44.6	X
35–44	X	-2.7	9.3	X	28.0	29.9	X	55.1	61.8
45–54	X	4.6	4.8	X	34.2	38.6	X	72.4	73.0
55–64	-14.4	-2.8	2.5	41.9	35.8	40.7	62.5	66.2	81.4

[1] ATL as % fatty streaks (F) plus raised lesions (R); FaF=F ÷ (100 - R); O–E in percentage units explained in

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
				the text; X indicates subgroups having fewer than five members.
Sorlie et al. (70)	139 autopsies of 9,824 Puerto Rican males aged 35–79	Interview with subject	Visual evaluation	Association of atherosclerosis in aorta with antemortem characteristics, simple correlation coefficients (Puerto Rican heart health program)

Characteristics measured at exam 1	Correlation coefficients: Total (120)	Rural (31)	Urban (89)
Systolic blood pressure	0.25	0.27	0.24
Diastolic blood pressure	0.19	0.29	0.16
Serum cholesterol	0.29	0.38	0.28
Age, exam 1	0.31	0.39	0.29
Relative weight	-0.08	-0.22	-0.06
Physical activity	-0.18	-0.21	-0.14
Blood glucose	0.14	0.05	0.17
Hematocrit	0.23	0.33	0.21
Education	-0.08	-0.23	-0.03
Income	0.01	-0.01	-0.01
Cigarettes smoked	0.32	0.37	0.31
Calories (24-hour recall)	-0.24	-0.55	-0.12
Starch (24-hour recall)	-0.19	-0.45	-0.07
Alcohol (24-hour recall)	-0.18	-0.39	-0.18
Total fats (24-hour recall)	-0.19	-0.49	-0.11
Triglycerides (fasting)	0.11	0.53	0.04
Ventricular rate	0.07	0.11	0.05
Vital capacity	-0.29	-0.28	-0.29

based on the findings in that study, as well as various interpretations of those findings, have been published. Strong and Richards (*74*) reported the basic findings on the association of cigarette smoking and aortic atherosclerosis in 1,320 autopsied men in New Orleans, 25 to 64 years of age. Aortic lesions were evaluated visually in coded specimens and objectively by analysis of radiographs. Interviewers obtained estimates of cigarette smoking habits of the deceased men from surviving relatives. Data were compared for black men and white men, and also were analyzed in groups according to the presence or absence of diseases thought to be associated with smoking or with coronary heart disease (emphysema, lung cancer, myocardial infarction, hypertension, diabetes mellitus, stroke, etc.). Atherosclerotic involvement of the aorta was greatest in heavy smokers and least in nonsmokers for both races in the total sample, as well as in the basal group (those cases least influenced by the bias of autopsy selection). The lesions were measured not only by visual evaluation, but also by optical electronic scanning of radiographic images of flattened arteries. Atherosclerotic lesions in the abdominal aorta were more extensive in the heavy smokers than in the nonsmokers, and there was an orderly trend of increased lesions with increased smoking. In general, the magnitude of difference in extent of lesions between nonsmokers and heavy smokers was greater in the abdominal aorta than in the coronary arteries. A variety of statistical analyses of smoking measures and atherosclerotic lesions was applied to determine the significance of the various differences and trends. All of the analyses confirmed that the differences between the heavy smokers and the nonsmokers in extent of raised atherosclerotic lesions were significant. A one-way multivariate analysis of nine atherosclerotic variables indicated that there were statistically significant differences among the three categories of smokers (heavy, light to moderate, and nonsmokers) for lesions in the abdominal aorta.

Following the initial report of Strong and Richards (*74*), there were three additional publications from this study. Two of these were directed toward interpretation of findings in regard to the effect of cigarette smoking on fatty streaks (the earliest grossly visible lesions of atherosclerosis) and raised atherosclerotic lesions (the more advanced stage of the atherosclerotic process). The other study was directed toward the interrelations of obesity, smoking, and atherosclerotic lesions in these same cases.

The original report by Strong and Richards (*74*) indicated that raised lesions, the more advanced lesions, were greater in heavy smokers than in nonsmokers. They also reported statistically significant differences for fatty streaks in the abdominal aorta and for fatty streaks in the coronary arteries, with the highest values in the nonsmokers and lowest values in the heavy smokers. The well-

recognized problem of evaluating fatty streaks when more advanced lesions of atherosclerosis are present made it difficult to interpret the findings on fatty streaks. Patel et al. (*54*) approached this problem by using a simple two-parameter model of fatty streaks arising from a normal intimal surface at a constant rate and with subsequent conversion to raised lesions at a constant rate. They concluded that in the abdominal aorta, smoking enhances the formation of fatty streaks as well as the subsequent conversions to more advanced lesions, and in the coronary arteries, smoking seems only to enhance the conversion of fatty streaks to fibrous plaques. Tracy et al. (*77*) evaluated the same data from the New Orleans study on smoking and atherosclerotic lesions. They approached the problem using a different model: $N \rightleftharpoons F \rightarrow R$, where N denotes normal intima, F denotes fatty streaks, and R denotes raised lesions. In this model, class A causes are viewed as promoting the process from beginning to end, while class B agents act at the first or the second step, but not at both. Their analysis and interpretation suggest that cigarette smoking has a large class B effect. They concluded that the target tissue of smoking is the fatty streak, and the slowly progressing or regressing fatty streak (formed alike in smokers and nonsmokers) is caused to progress more rapidly or to cease to regress by smoking. Both of these studies, Patel et al. (*54*) and Tracy et al. (*77*), agree that smoking has a role in the progression of fatty streaks to a more advanced stage of the atherosclerotic process.

Auerbach and Garfinkel in 1980 (*5*) published findings on smoking habits and atherosclerotic lesions in over 1,400 aortas collected at autopsy from male patients. The extent of atherosclerotic lesions (plaques, ulcerations, and calcification) increased with number of cigarettes smoked, and was also greater in ex-cigarette smokers and pipe smokers than in nonsmokers. The findings were more striking in the abdominal aorta than in the thoracic aorta. Aortic aneurysms were found eight times more frequently among those who smoked one to two packs of cigarettes per day than in nonsmokers.

Lifšic (*37*) reported on the relationship of cigarette smoking to aortic lesions based on the Yalta sample from the World Health Organization (WHO) autopsy study of five cities in Europe (*87*). Information on cigarette smoking was obtained by means of interviews with the subjects' near relatives. The prevalence and extent of atherosclerotic lesions were evaluated in autopsies of 865 men, aged 20 to 79 years, out of 1,220 deaths occurring in Yalta residents of this age and sex group during the period of study. There were significant positive relationships between smoking and the extent of fibrous plaques, complicated lesions, and calcified lesions in the abdominal aorta.

Aortic atherosclerosis has also been evaluated using autopsy followup of prospective epidemiologic studies of cardiovascular disease. Epidemiological studies in Puerto Rico and Honolulu documented selected risk factors, including cigarette smoking habits, during life and had standardized evaluation of atherosclerotic lesions at autopsy (*56, 70*). Each of these studies reported findings on the relationship of risk factors and aortic atherosclerotic lesions in more than 100 deceased men from large cohorts that had been examined and followed during life. A smaller study from Malmö, Sweden, had some of the same features as these larger studies (*71*). All of these studies found a significant positive relationship between cigarette smoking and aortic atherosclerosis.

The prospective epidemiologic studies with autopsy followup confirmed the relationship between smoking and atherosclerotic aortic lesions found in earlier autopsy studies. The preponderance of evidence suggests that cigarette smoking aggravates or accelerates aortic atherosclerosis, and this effect on atherosclerosis may be more pronounced in the aorta than in the coronary arteries.

Cerebral Vasculature

The relationship between cigarette smoking and atherosclerosis in the cerebral vasculature has not been extensively evaluated. Two studies that have examined this question are summarized in Table 4. Sternby (*71*) reported that cigarette smokers had more extensive raised lesions in the basilar artery than had nonsmokers. This study was based on 60 autopsy subjects from 703 men born in 1914 who participated in a study of cardiovascular disease in Malmö, Sweden. Holme et al. (*29*) reported a positive correlation coefficient between raised lesions in the cerebral vessels and the number of cigarettes smoked; this relationship was not statistically significant, however.

The limited amount of information available on the relationship between cigarette smoking and atherosclerosis in the cerebral vasculature does not allow a clear conclusion to be drawn at this time.

Pathophysiologic Mechanisms of Tobacco Smoke

Studies of Components of Tobacco Smoke

The possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking were reviewed in the 1971 Report of the Surgeon General *The Health Consequences of Smoking* (*80*). The major components of cigarette smoke considered in that review were nicotine and carbon monoxide. Numerous investigators have studied the effect of nicotine administration, either subcutaneously or intravenously, upon experimentally induced changes in the aorta and coronary arteries of animals. When administered alone, nicotine

TABLE 4.—Autopsy studies of atherosclerosis involving cerebral vasulation

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Sternby (77)	60 autopsied subjects from 703 males in CHD study in Malmo, Sweden	Interview with subject	Visual inspection	Smoking and atherosclerosis in the basilar arteries Smoking category / Number / Basilar artery raised lesions Non: 3 / 1 Ex: 8 / 6 Light: 18 / 3 Heavy: 17 / 7
Holme et al. (29)	129 autopsies out of 16,200 men aged 40–49 in Oslo CHD study	Interview with subject	Visual grading	Correlation coefficient between raised lesions in the cerebral vessels and number of cigarettes smoked per day is 0.090 (not statistically significant).

induces certain degenerative or necrotic changes in the arterial wall, but these are characteristically medial changes rather than the intimal changes that characterize atherosclerosis. When nicotine is administered in combination with a high cholesterol diet, it seems to aggravate arterial damage, according to a preponderance of studies. Some studies, however, do not report this synergism between cholesterol feeding and nicotine (*16, 84*).

Schievelbein and associates (*66*) reported the effect of long-term nicotine exposure on the development of arteriosclerosis in rabbits. They administered nicotine to rabbits not being fed an atherogenic diet. All animals had arteriosclerotic lesions in the aorta and coronary arteries at the end of the experiment, but there was no difference between the control group and the experimental animals administered nicotine. They reviewed the experiments of several authors who studied nicotine and their own animal experiments and concluded that the evidence did not establish a causative role for nicotine in the etiology of arteriosclerosis.

A recent report by Liu et al. (*38*) on experimental arterial lesions in rhesus monkeys with various combinations of dietary hypercholesterolemia, hypervitaminosis D(2), and nicotine indicated that the combination of these three factors produced high scores for various measures of arteriosclerotic changes in aorta, coronary, and limb arteries of the monkeys. When the factors were administered singly, however, very little arterial disease was demonstrated over the period of the experiment. The group with all three factors was the only group with significant coronary arteriosclerosis as well as complicated lesions of the arteries of extremities.

Booyse et al. (*15*) reported the effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. They found that fasting serum levels of glucose, triglyceride, total cholesterol, and LDL cholesterol were elevated in nicotine-treated rabbits as compared with controls. They found no significant differences between the experimental group and the controls for leukocyte, erythrocyte, and platelet counts, or for hematocrit and hemoglobin. Endothelial cells from the aortic arch of the nicotine-treated animals showed extensive changes, such as increased cytoplasmic silver deposition, increased formation of microvilli, and numerous focal areas of "ruffled" endothelium. The authors concluded that nicotine administered orally to rabbits has a demonstrable morphologic effect on endothelial cells in the aortic arch.

While the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive, nicotine is certainly one of the components of tobacco smoke for which there are both some supporting data and a rational conceptualization for a role in the pathogenesis of atherosclerotic lesions. There is little doubt that nicotine alone or in combination with other

factors, such as hypercholesterolemia or excessive doses of vitamin D, can damage the arterial wall, and arterial injury is widely accepted as one mechanism for predisposing to or accelerating lesions in animal models of atherosclerosis.

Carbon monoxide is another major component of cigarette smoke for which there are some data supporting a possible atherogenic role; however, a review of recent literature on the role of carbon monoxide in arterial injury and atherogenesis leads to no consensus. Early studies by Astrup and coworkers (*3*) on the effect of carbon monoxide in rabbits suggested the theory that carbon monoxide causes endothelial damage, which might promote atherogenesis. Later studies by Astrup's group (*2, 32*) indicated that the duration of exposure of rabbits to carbon monoxide did not influence the intimal morphology of the coronary arteries or the aorta. They felt that these new data contradicted the theory of carbon-monoxide-mediated endothelial damage as a cause of atherosclerosis.

Recent experimental studies have produced a variety of results regarding the effects of carbon monoxide on the development of arterial lesions. Malinow et al. (*40*) exposed cynomolgus monkeys, fed a standard laboratory diet or a semipurified high cholesterol diet, to carbon monoxide or to room air for 14 months. None of the animals developed a myocardial infarction, and there was no difference in plasma cholesterol levels or in aortic or coronary atherosclerosis attributable to carbon monoxide exposure. Davies et al. (*17*) studied the effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit and found there was an increase in coronary artery atherosclerosis in the carbon-monoxide-exposed animals, but they did not find significant differences in the lipid content of the aortas. Armitage et al. (*1*) studied the effect of carbon monoxide on the development of atherosclerosis in the White Carneau pigeon and found that the severity of coronary atherosclerosis was significantly greater in birds exposed to carbon monoxide than in nonexposed birds after 52 weeks of exposure, but not after 84 weeks. The severity of atherosclerosis was related to the degree of hypercholesterolemia. They suggested that in the White Carneau pigeon, exposure to carbon monoxide elevates plasma cholesterol levels, and thereby increases the extent of experimentally induced atherosclerotic lesions. They further suggested that compensatory mechanisms may reduce the effect of carbon monoxide exposure on hypercholesterolemia over time.

Two reviews in 1979 came to different conclusions concerning the relationship of carbon monoxide and arteriosclerosis. Astrup and Kjeldsen (*2*) surveyed the cardiovascular effects of exposure of animals to carbon monoxide and concluded that carbon monoxide produces myocardial effects that can lead to decreased myocardial oxygen tension with compensatory increases in coronary blood flow.

They stated that their previous findings of arterial intimal changes had not been confirmed. Turner (*78*) reviewed studies involving carbon monoxide, tobacco smoking, and the pathogenesis of atherosclerosis, and concluded that carbon monoxide exposure enhances the extent of coronary atherosclerosis in pigeons that have been made hypercholesterolemic by adding dietary cholesterol. Carbon monoxide was without effect on normocholesterolemic birds. They indicated that the level of carbon monoxide exposure, the duration of exposure, and the level of dietary cholesterol are critically interdependent factors that can influence the pathogenesis of the disease.

Studies by Sarma et al. (*62*) on the effect of carbon monoxide on lipid metabolism of human coronary arteries provide some support for the idea that carbon monoxide increases endothelial permeability. They perfused human coronary arteries under sterile conditions in vitro with blood containing high and low concentrations of carbon monoxide. They found no effect of carbon monoxide on lipid synthesis in the arterial wall; however, the arteries that were exposed to carbon monoxide showed a higher uptake of cholesterol from the perfusate as compared with their corresponding controls. Thus, the results of Sarma et al. (*62*) were in agreement with those of other investigators who have found that carbon monoxide significantly increases the permeability of endothelial membranes.

Schneiderman and Goldstick (*67*) used a computer simulation of the oxygen transport system of the arterial wall to evaluate the extent of carbon-monoxide-induced hypoxia of the arterial wall under various conditions; the results suggested that the moderate to high carboxyhemoglobin levels found in some smokers may result in a significant reduction in the oxygen tension of the arterial wall.

Hugod (*31*) reported no morphological change in the coronary arteries and aortas of rabbits exposed to low doses of hydrogen cyanide, alone or in combination with 200 ppm carbon monoxide, and nitric oxide for 2 weeks.

McMillan (*46*) reviewed the many substances that may enter the body from tobacco smoke and that have been conjectured as having a role in cardiovascular disease. He concentrated on those substances other than carbon monoxide and nicotine, such as cadmium, zinc, chromium, carbon disulfide, carbon dioxide, tobacco antigens, hydrogen cyanide, nitric oxide, and polonium-210. He concluded that these substances provide interesting ground for speculation as to their possible role in cardiovascular disease, but that only carbon monoxide and nicotine offer both data and a rational conceptualization for a role in cardiovascular disease.

Studies of Whole Tobacco Smoke

McGill (*42*) reviewed potential mechanisms for the augmentation of atherosclerosis and atherosclerotic disease by cigarette smoking.

On the basis of his review of the evidence concerning smoking and serum lipid and lipoprotein concentrations, he suggested that cigarette smoking often causes a slight to moderate elevation of total serum cholesterol concentration, and that smoking may depress HDL concentrations and elevate LDL concentrations. These changes might have the effect of increasing atherosclerosis because increased levels of LDL and decreased levels of HDL have been shown to be related to increased amounts of atherosclerosis as well as to an increased risk of coronary heart disease.

Hojnacki et al. (*28*) studied the effect of acute inhalation of cigarette smoke and consumption of dietary cholesterol on plasma lipoprotein composition in atherosclerosis-susceptible White Carneau pigeons. They concluded that cigarette smoking can mediate alterations in lipoprotein composition independent of changes induced by dietary cholesterol and saturated fat.

Sieffert et al. (*69*) demonstrated endothelial damage and focal platelet aggregation after exposing Sprague-Dawley rats to tobacco smoke for 15-minute periods three times a day for 6 and 12 weeks. Scanning electron microscopic examination of perfusion-fixed thoracic aortas disclosed elongation of endothelial cells, uplifting of endothelial cells from the basement membrane, areas of endothelial loss, pitting, crater formation, and white blood cell invasion of the underlying intima. They also found platelet aggregation on damaged intima. They did not indicate which one of the constituents of tobacco smoke they suspected as being the cause of these changes.

Rogers et al. (*58*) recently completed an investigation of cigarette smoking, diet-induced hyperlipidemia, and experimental atherosclerosis in baboons. The design of the study and interim results are contained in a report by Rogers et al. (*57*). The baboons in this controlled experiment consumed a diet enriched in cholesterol and saturated fat for 3.3 years and puffed on lighted cigarettes or shams for 2.8 years. The study was designed to determine whether cigarette smoking interacts with diet-induced hyperlipidemia to accelerate the development of atherosclerosis. This hypothesis was based on a report by Keys (*35*), who found that populations with high total serum cholesterol concentrations and a high incidence of atherosclerotic disease have a dose-related relationship between cigarette smoking and the incidence of atherosclerotic disease. However, in populations with low total serum cholesterol levels and a low incidence of atherosclerotic disease, cigarette smoking is not associated with the incidence of atherosclerotic disease. Thus, cigarette smoking might augment atherosclerosis only when it interacts with an atherogenic diet. The investigation by Rogers et al. (*57, 58*), used nonhuman primates—baboons—as experimental animals, and the animals were trained by operant conditioning techniques to smoke cigarettes in a human-like manner. The diet induced a moderate

hypercholesterolemia, which attained a peak of 235 mg/dl 5 months after initiation and declined thereafter to 160 mg/dl at termination. The early report of Rogers et al. (*57*) disclosed no significant differences in serum lipids or lipoproteins between smokers and shams after 1.6 years of smoking; however, there were some differences that would be expected to accompany the augmentation of atherosclerosis, namely higher LDL/HDL ratios in smokers than in shams. At the completion of the experiment, these trends of differences in lipoprotein concentrations were not present, and the mean serum total cholesterol, serum triglyceride, LDL cholesterol, and HDL cholesterol concentrations of smokers and shams were not significantly different. The LDL/HDL cholesterol ratios of smokers and shams were almost identical. Their observations on LDL/HDL cholesterol ratios in the midcourse of the experiment and again at the end suggested that cigarette smoking either increases the LDL/HDL cholesterol ratio only during hypercholesterolemia or increases the LDL/HDL ratio only in some animals.

At autopsy of these baboons, the mean extent of fatty streaks was not significantly different for smokers versus shams in the aorta, femoral, iliac, and innominate arteries. The mean extent of fatty streaks in smokers was significantly greater than in shams for the carotid arteries. The variability in extent of lesions was greater in smokers than in shams, suggesting the possibility that a subset of smokers may have responded positively to smoking by developing increased lesions. This difference in variability of lesions was statistically significant for the thoracic aorta, carotid, and innominate arteries. The authors suggest that the "compensatory" decline in mean serum cholesterol concentration that occurred in the latter part of the experiment could have led to regression of experimentally induced lesions.

The authors indicate that their results do not support the hypothesis that cigarette smoking, at a level approximately equivalent to that of the average human cigarette smoker, augments experimental atherosclerosis in the presence of a moderate level of diet-induced hypercholesterolemia. They did, however, find a significantly greater extent of fatty streaks in the carotid arteries for the smokers and significantly more variability in the extent of lesions in the smokers. Also, among the small number of animals that died during the course of the experiment, the smoking animals had more extensive involvement with lesions than did the shams. Nevertheless, there were no dramatic, clear-cut, across-the-board differences between the smoking and nonsmoking animals. The authors conclude that this experiment cannot be regarded as a conclusive test of the hypothesis that cigarette smoking can augment the formation of fatty streaks associated with dietary-induced hyperlipidemia.

McGill's review (*42*) indicated that smokers have slightly increased erythrocyte counts, hematocrit, and hemoglobin concentrations, but he doubted that the slight changes observed would increase the risk of atherosclerosis. In the experiments with baboons, smokers also had elevated leukocyte counts owing to both increased polymorphonuclear leukocytes and increased lymphocytes. These changes might be one manifestation of an altered immune system that might deserve attention as a possible mechanism for accelerating atherogenesis. The smoking baboons had slightly elevated blood glucose levels; it is not known if this change would contribute to atherosclerosis. Body weight and blood pressure are slightly lower in smokers than in nonsmokers, and this response to smoking is in the opposite direction with regard to risk of atherosclerotic disease.

Smoking and the Hemostatic System

McGill indicated that the limited number of recent studies of the effects of smoking on the hemostatic system show little or no effect on clotting action, but marked effects on platelets. Platelet counts are not different in smokers and nonsmokers, but smokers have a decrease in survival time and an increase in platelet turnover (*50*), increased adhesiveness (*49*), and increased tendency for aggregation (*24, 27, 36*).

Ogston et al. (*52*) found that chronic smoking led to an increased plasma fibrinogen concentration, but acute smoking did not. Janzon and Nilsson (*33*) found that chronic smoking was associated with increased fibrinolytic activity of the blood.

Davis and Davis (*18*) studied the effect of cigarette smoking on circulating platelet aggregates as detected by the platelet-aggregate ratio in volunteer subjects. The platelet-aggregate ratios were lower in the smokers, indicating increased circulating platelet aggregates. The authors indicated that the decrease in platelet-aggregate ratio was not mediated through the elevation of plasma nonesterified fatty acid concentration.

Fuster et al. (*21*) found a shortened platelet survival half-life in apparently normal persons who smoked and in persons with a strong family history of coronary disease. Their study suggested a possible relationship among cigarette smoking, strong family history of coronary disease, and platelet activation in the process of coronary atherogenesis in the young adult.

Smoking and the Immune System

McGill (*42*) suggested that the leukocytosis observed in smokers may represent in part a manifestation of an immune disorder. Immune complex disease markedly aggravates atherogenesis in rabbits (*48*) and in baboons (*30*). Becker and Dubin (*10*) and Becker et al. (*11*) have identified a low molecular weight glycoprotein in

tobacco smoke that is highly antigenic in man. McGill (*42*) suggests that differences in sensitivity to antigenic materials could account for the great variation in response to cigarette smoking. He also suggests endothelial injury and increased endothelial permeability as a mechanism for cigarette smoking effects on cardiovascular disease. Becker (*9*), in summarizing a workshop on immunologic injury and the thrombotic process in atherogenesis, postulated that the capacity of tobacco glycoprotein to activate the intrinsic pathway of coagulation might contribute to the growth of arteriosclerotic plaques and to more lethal complications by initiating thrombus formation. Denburg et al. (*19*) studied the reactivity of 164 patients with peripheral vascular disease to purified tobacco glycoprotein; they suggested that reactivity to tobacco glycoprotein may be causally related to the development of atherosclerotic vascular disease.

Conclusions

1. A preponderance of evidence both from prospective studies with autopsy followup and from autopsy studies with retrospective smoking data indicates that cigarette smoking has a significant positive association with atherosclerosis. This evidence suggests that cigarette smoking has the effect of aggravating and accelerating the development of atherosclerotic lesions in the artery wall and that its effect is not limited to those events related to the occlusive episode. The effects are most striking for aortic atherosclerosis; a significant positive relationship also exists between cigarette smoking and atherosclerotic lesions in the coronary arteries, at least for most high risk populations. Cigarette smoking could also be associated with other factors that precipitate thrombosis, hemorrhage, or vasoconstriction leading to occlusion and ischemia.
2. Some evidence exists that cigarette smoke alters total serum cholesterol concentrations and lipoprotein composition in ways that would be expected to increase the development of atherosclerosis. Recent studies of the effects of smoking on the hemostatic system indicate effects of smoking on platelet function.
3. Although the specific mechanisms by which tobacco smoke affects arteriosclerosis have not been clearly delineated, the effects of cigarette smoking on the atherosclerotic lesions that underlie cardiovascular disease seem well established.

References

(1) ARMITAGE, A.K., DAVIES, R.F., TURNER, D.M. The effects of carbon monoxide on the development of atherosclerosis in the White Carneau pigeon. *Atherosclerosis* 23(2): 333–344, March-April 1976.

(2) ASTRUP, P., KJELDSEN, K. Model studies linking carbon monoxide and/or nicotine to arteriosclerosis and cardiovascular disease. *Preventive Medicine* 8(3): 295–302, May 1979.

(3) ASTRUP, P., KJELDSEN, K., WANSTRUP, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. *Journal of Atherosclerosis Research* 7(3): 343–354, May-June 1967.

(4) AUERBACH, O., CARTER, H.W., GARFINKEL, L., HAMMOND, E.C. Cigarette smoking and coronary artery disease: A macroscopic and microscopic study. *Chest* 70(6): 697–705, December 1976.

(5) AUERBACH, O., GARFINKEL, L. Atherosclerosis and aneurysm of the aorta in relation to smoking habits and age. *Chest* 78(6): 805–809, December 1980.

(6) AUERBACH, O., HAMMOND, E.C., GARFINKEL, L. Smoking in relation to atherosclerosis of the coronary arteries. *New England Journal of Medicine* 273(15): 775–779, October 7, 1965.

(7) AUERBACH, O., HAMMOND, E.C., GARFINKEL, L., KIRMAN, D. Thickness of walls of myocardial arterioles in relation to smoking and age. *Archives of Environmental Health* 22(1): 20–27, January 1971.

(8) AVTANDILOV, G.G., KOLENOVA, V.I., PONOMARENKO, O.V. Kureniye tabaka i stepen' ateroskleroticheskogo porazheniya koronarnykh arteriy serdtsa i aorty. [Tobacco smoking and the degree of atherosclerotic lesions of coronary arteries of the heart and aorta.] *Kardiologiya* 5(1): 30–34, January-February 1965.

(9) BECKER, C.G. Summary of Workshop 3b: Immunologic injury. In: Chandler, A.B., Eurenius, K., McMillan, G.C., Nelson, C.B., Schwartz, C.J., Wessler, S. (Editors). *The Thrombotic Process in Atherogenesis.* New York, Plenum Press, 1978, pp. 371–382.

(10) BECKER, C.G., DUBIN, T. Activation of factor XII by tobacco glycoprotein. *Journal of Experimental Medicine* 146(2): 457–467, August 1, 1977.

(11) BECKER, C.G., DUBIN, T., WIEDEMANN, H.P. Hypersensitivity to tobacco antigen. *Proceedings of the National Academy of Sciences of the United States of America* 73: 1712–1716, May 1976.

(12) BENDITT, E.P. Evidence for a monoclonal origin of human atherosclerotic plaques and some implications. *Circulation* 50(4): 650–652, October 1974.

(13) BENDITT, E.P. The origin of atherosclerosis. *Scientific American* 236(2): 74–85, February 1977.

(14) BENDITT, E.P., BENDITT, J.M. Evidence for a monoclonal origin of human atherosclerotic plaques. *Proceedings of the National Academy of Sciences of the United States of America* 70(6): 1753–1756, June 1973.

(15) BOOYSE, F.M., OSIKOWICZ, G., QUARFOOT, A.J. Effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. *American Journal of Pathology* 102(2): 229–238, February 1981.

(16) CHOI, Y.Y. Effect of nicotine upon cholesterol-induced atherosclerosis in rabbits. *New Medical Journal* 10(7): 685–693, 1967.

(17) DAVIES, R.F., TOPPING, D.L., TURNER, D.M. The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. *Atherosclerosis* 24(3): 527–536, September 1976.

(18) DAVIS, J.W., DAVIS, R.F. Acute effect of tobacco cigarette smoking on the platelet aggregate ratio. *American Journal of the Medical Sciences* 278(2): 139–143, September-October 1979.

(19) DENBURG, J., BLAJCHMAN, J., GAULDIE, J., HORSEWOOD, P., GILL, G., THOMSON, G., BEATTIE, H., EVANS, G., BIENENSTOCK, J. Hypersensitivity to tobacco glycoprotein in human peripheral vascular disease. *Annals of Allergy* 47(1): 8–13, July 1981.

(20) DUFF, G.L., McMILLAN, G.C. Pathology of atherosclerosis. *American Journal of Medicine* 11(1): 92–108, 1951.

(21) FUSTER, V., CHESEBRO, J.H., FRYE, R.L., ELVEBACK, L.R. Platelet survival and the development of coronary artery disease in the young adult: Effects of cigarette smoking, strong family history and medical therapy. *Circulation* 63(3): 546–551, March 1981.

(22) GEER, J.C., HAUST, M.D. Smooth muscle cells in atherosclerosis. In: Pollak, O.J., Simms, H.S., Kirk, J.E. (Editors). *Monographs on Atherosclerosis*, Volume 2. Basel, S. Karger, 1972, 140 pp.

(23) GLAGOV, S., OZOA, A.K. Significance of the relatively low incidence of atherosclerosis in the pulmonary, renal, and mesenteric arteries. *Annals of the New York Academy of Sciences* 149(2): 940–955, November 21, 1968.

(24) GLYNN, M.F., MUSTARD, J.F., BUCHANAN, M.R., MURPHY, E.A. Cigarette smoking and platelet aggregation. *Canadian Medical Association Journal* 95(10): 549–553, September 3, 1966.

(25) GOTTO, A.M., Jr., SMITH, L.C., ALLEN, B. (Editors). *Atherosclerosis V: Proceedings of the Fifth International Symposium on Atherosclerosis.* Houston, November 6–9, 1979, New York, Springer-Verlag, 1980, 843 pp.

(26) HATANO, S., MATSUZAKI, T. Atherosclerosis in relation to personal attributes of a Japanese population in homes for the aged. In: Schettler, G., Goto, Y., Hata, Y., Klose, G. (Editors). *Atherosclerosis IV: Proceedings of the Fourth International Symposium on Atherosclerosis.* Tokyo, August 24–28, 1976, Berlin, Springer-Verlag, 1977, pp. 116–120.

(27) HAWKINS, R.I. Smoking, platelets and thrombosis. *Nature* 236(5348): 450–452, April 28, 1972.

(28) HOJNACKI, J.L., MULLIGAN, J.J., CLUETTE, J.E., KEW, R.R., STACK, D.J., HUBER, G.L. Effect of cigarette smoke and dietary cholesterol on plasma lipoprotein composition. *Artery* 9(4): 285–304, 1981.

(29) HOLME, I., ENGER, S.C., HELGELAND, A., HJERMANN, I., LEREN, P., LUND-LARSEN, P.G., SOLBERG, L.A., STRONG, J.P. Risk factors and raised atherosclerotic lesions in coronary and cerebral arteries. Statistical analysis from the Oslo study. *Arteriosclerosis* 1(4): 250–256, July-August 1981.

(30) HOWARD, A.N., PATELSKI, J., BOWYER, D.E., GRESHAM, G.A. Atherosclerosis induced in hypercholesterolaemic baboons by immunological injury, and the effects of intravenous polyunsaturated phosphatidyl choline. *Atherosclerosis* 14(1): 17–29, July-August 1971.

(31) HUGOD, C. Effect of exposure to 0.5 ppm hydrogen cyanide singly or combined with 200 ppm carbon monoxide and/or 5 ppm nitric oxide on coronary arteries, aorta, pulmonary artery, and lungs in the rabbit. *International Archives of Occupational and Environmental Health* 44(1): 13–23, 1979.

(32) HUGOD, C., HAWKINS, L.H., KJELDSEN, K., THOMSEN, H.K., ASTRUP, P. Effect of carbon monoxide exposure on aortic and coronary intimal morphology in the rabbit. A revaluation. *Atherosclerosis* 30(4): 333–342, August 1978.

(33) JANZON, L., NILSSON, I.M. Smoking and fibrinolysis. *Circulation* 51(6): 1120–1123, June 1975.

(34) JONES, R.J. (Editor). *Atherosclerosis: Proceedings of the Second International Symposium on Atherosclerosis.* Chicago, November 2–5, 1969. New York, Springer-Verlag, 1970, 706 pp.

(35) KEYS, A. Smoking habits. In: Keys, A. (Editor). *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease.* Cambridge, Harvard University Press, 1980, pp. 136–160.

(36) LEVINE, P.H. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. *Circulation* 48(3): 619–623, September 1973.

(37) LIFŠIC, A.M. Atherosclerosis in smokers. *Bulletin of the World Health Organization* 53(5/6): 631–638, 1976.

(38) LIU, L.B., TAYLOR, C.B., PENG, S.K., MIKKELSON, B. Experimental arteriosclerosis in Rhesus monkeys induced by multiple risk factors: Cholesterol, vitamin D, and nicotine. *Arterial Wall* 5(1): 25–31, 33, 35, and 37, 1979.

(39) LONG, E.R. Development of our knowledge of arteriosclerosis. In: Blumenthal, H.T. (Editor). *Cowdry's Arteriosclerosis. A Survey of the Problem.* Second edition. Springfield, Illinois, Charles C. Thomas, 1967, pp. 5–20.

(40) MALINOW, M.R., McLAUGHLIN, P., DHINDSA, D.S., METCALFE, J., OCHSNER, A.J., III, HILL, J., McNULTY, W.P. Failure of carbon monoxide to induce myocardial infarction in cholesterol-fed cynomolgus monkeys (*Macaca fascicularis*). *Cardiovascular Research* 10(1): 101–108, January 1976.

(41) McGILL, H.C., Jr. (Editor). The geographic pathology of atherosclerosis. *Laboratory Investigation* 18(5): 463–653, May 1968.

(42) McGILL, H.C., Jr. Potential mechanisms for the augmentation of atherosclerosis and atherosclerotic disease by cigarette smoking. *Preventive Medicine* 8(3): 390–403, May 1979.

(43) McGILL, H.C., Jr., ARIAS-STELLA, J., CARBONELL, L.M., CORREA, P., de VEYRA, E.A., Jr., DONOSO, S., EGGEN, D.A., GALINDO, L., GUZMAN, M.A., LICHTENBERGER, E., LOKEN, A.C., McGARRY, P.A., McMAHAN, C.A., MONTENEGRO, M.R., MOOSSY, J., PEREZ-TAMAYO, R., RESTREPO, C., ROBERTSON, W.B., SALAS, J., SOLBERG, L.A., STRONG, J.P., TEJADA, C., WAINRIGHT, J. General findings of the International Atherosclerosis Project. *Laboratory Investigation* 18(5): 498–502, May 1968.

(44) McGILL, H.C., Jr., EGGEN, D.A., STRONG, J.P. Atherosclerotic lesions in the aorta and coronary arteries of man. In: Roberts, J.C., Jr., Straus, R. (Editors). *Comparative Atherosclerosis.* New York, Harper & Row, 1965, pp. 311–326.

(45) McMAHAN, C.A., RICHARDS, M.L., STRONG, J.P. Individual cigarette usage: Self-reported data as a function of respondent-reported data. *Atherosclerosis* 23(3): 477–488, May/June 1976.

(46) McMILLAN, G.C. Evidence for components other than carbon monoxide and nicotine as etiological factors in cardiovascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker.* Volume 1. Proceedings of the Third World Conference on Smoking and Health, New York, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 363–367.

(47) McMILLAN, G.C. Atherogenesis: The process from normal to lesion. In: Chandler, A.B., Eurenius, K., McMillan, G.C., Nelson, C.B., Schwartz, C.J., Wessler, S. (Editors). *The Thrombotic Process in Atherogenesis.* New York, Plenum Press, 1978, pp. 3–10.

(48) MINICK, C.R., MURPHY, G.E., CAMPBELL, W.G., Jr. Experimental induction of athero-arteriosclerosis by the synergy of allergic injury to arteries and lipid-rich diet. I. Effect of repeated injections of horse serum in rabbits fed a dietary cholesterol supplement. *Journal of Experimental Medicine* 124(4): 635–652, October 1, 1966.

(49) MURCHISON, L.E., FYFE, T. Effects of cigarette smoking on serum-lipids, blood-glucose, and platelet adhesiveness. *Lancet* 2(7456): 182–184, July 23, 1966.

(50) MUSTARD, J.F., MURPHY, E.A. Effect of smoking on blood coagulation and platelet survival in man. *British Medical Journal* 1(5334): 846–849, March 30, 1963.

(51) NAEYE, R.L., TRUONG, L.D. Effects of cigarette smoking on intramyocardial arteries and arterioles in man. *American Journal of Clinical Pathology* 68(4): 493–498, October 1977.

(52) OGSTON, D., BENNETT, N.B., OGSTON, C.M. The influence of cigarette smoking on the plasma fibrinogen concentration. *Atherosclerosis* 11(2): 349–352, March/April 1970.

(53) PATEL, Y.C., EGGEN, D.A., STRONG, J.P. Obesity, smoking and atherosclerosis. A study of interassociations. *Atherosclerosis* 36(4): 481–490, August 1980.

(54) PATEL, Y.C., KODLIN, D., STRONG, J.P. On the interpretation of smoking risks in atherosclerosis. *Journal of Chronic Diseases* 33(3): 147–155, 1980.

(55) PEARSON, T.A., WANG, A., SOLEZ, K., HEPTINSTALL, R.H. Clonal characteristics of fibrous plaques and fatty streaks from human aortas. *American Journal of Pathology* 81(2): 379–388, November 1975.

(56) RHOADS, G.G., BLACKWELDER, W.C., STEMMERMANN, G.N., HAYASHI, T., KAGAN, A. Coronary risk factors and autopsy findings in Japanese-American men. *Laboratory Investigation* 38(3): 304–311, March 1978.

(57) ROGERS, W.R., BASS, III, R.L., JOHNSON, D.E., KRUSKI, A.W., McMAHAN, C.A., MONTIEL, M.M., MOTT, G.E., WILBUR, R.L., McGILL, H.C., Jr. Atherosclerosis-related responses to cigarette smoking in the baboon. *Circulation* 61(6): 1188–1193, June 1980.

(58) ROGERS, W.R., CAREY, K.D., McMAHAN, C.A., MONTIEL, M.M., MOTT, G.E., NULTON, C.P., McGILL, H.C., Jr. *Cigarette Smoking, Dietary Hyperlipidemia and Experimental Atherosclerosis in the Baboon.* Unpublished manuscript.

(59) ROSS, R., GLOMSET, J.A. The pathogenesis of atherosclerosis (second of two parts). *New England Journal of Medicine* 295(8): 420–425, August 19, 1976.

(60) SACKETT, D.L., GIBSON, R.W., BROSS, I.D.J., PICKREN, J.W. Relation between aortic atherosclerosis and the use of cigarettes and alcohol. *New England Journal of Medicine* 279(26): 1413–1420, December 26, 1968.

(61) SACKETT, D.L., WINKELSTEIN, W., Jr. The relationship between cigarette usage and aortic atherosclerosis. *American Journal of Epidemiology* 86(1): 264–270, July 1967.

(62) SARMA, J.S.M., TILLMANNS, H., IKEDA, S., BING, R.J. The effect of carbon monoxide on lipid metabolism of human coronary arteries *Atherosclerosis* 22(2): 193–198, September-October 1975.

(63) SCHETTLER, G., GOTO, Y., HATA, Y., KLOSE, G. (Editors). *Atherosclerosis IV.* Proceedings of the Fourth International Symposium on Atherosclerosis, Tokyo, August 24–28, 1976. Berlin, Springer-Verlag, 1977, 797 pp.

(64) SCHETTLER, G., GOTTO, A.M., Jr., SCHLIERF, G. (Editors). *Atherosclerosis VI.* Proceedings of the Sixth International Symposium on Atherosclerosis. Berlin, Springer-Verlag, in press.

(65) SCHETTLER, G., WEIZEL, A. (Editors). *Atherosclerosis III.* Proceedings of the Third International Symposium on Atherosclerosis, West Berlin, October 24–28, 1973. Berlin, Springer-Verlag, 1974, 1034 pp.

(66) SCHIEVELBEIN, H., LONDONG, V., LONDONG, W., GRUMBACH, H., REMPLIK, V., SCHAUER, A., IMMICH, H. Nicotine and arteriosclerosis. An experimental contribution to the influence of nicotine on fat metabolism. *Zeitschrift für Klinische Chemie und Klinische Biochemie* 8(3): 190–196, May 1970.

(67) SCHNEIDERMAN, G., GOLDSTICK, T.K. Computer simulation of the human thoracic aorta to evaluate the possible role of smoking in atherogenesis. *Advances in Experimental Medicine and Biology* 94: 407–412, July 1977.

(68) SCHWARTZ, C.J., MITCHELL, J.R.A. Observations on localization of arterial plaques. *Circulation Research* 11(1): 63–63, July 1962.

(69) SIEFFERT, G.F., KEOWN, K., MOORE, W.S. Pathologic effect of tobacco smoke inhalation on arterial intima. *Surgical Forum* 32: 333–335, 1981.

(70) SORLIE, P.D., GARCIA-PALMIERI, M.R., CASTILLO-STAAB, M.I., COSTAS, R., Jr., OALMANN, M.C., HAVLIK, R. The relation of antemortem factors to atherosclerosis at autopsy. The Puerto Rico Heart Health Program. *American Journal of Pathology* 103(3): 345–352, June 1981.

(71) STERNBY, N.H. Atherosclerosis, smoking and other risk factors. In: Gotto, A.M., Jr., Smith, L.C., Allen, B. (Editors). *Atherosclerosis V.* Proceedings of the Fifth International Symposium on Atherosclerosis, Houston, Texas, November 6–9, 1979. New York, Springer-Verlag, 1980, pp. 67–70.

(72) STRONG, J.P., EGGEN, D.A., OALMANN, M.C. The natural history, geographic pathology, and epidemiology of atherosclerosis. In: Wissler, R.W., Geer, J.C. (Editors). *The Pathogenesis of Atherosclerosis.* Baltimore, Williams & Wilkins Company, 1972, pp. 20–40.

(73) STRONG, J.P., EGGEN, D.A., TRACY, R.E. The geographic pathology and topography of atherosclerosis and risk factors for atherosclerotic lesions. In: Chandler, A.B., Eurenius, K., McMillan, G.C., Nelson, C.B., Schwartz, C.J., Wessler, S. (Editors). *The Thrombotic Process in Atherogenesis.* Advances in Experimental Biology. Volume 104. New York, Plenum Press, 1978, pp. 11–31.

(74) STRONG, J.P. RICHARDS, M.L. Cigarette smoking and atherosclerosis in autopsied men. *Atherosclerosis* 23(3): 451–476, May-June, 1976.

(75) STRONG, J.P., RICHARDS, M.L., McGILL, H.C., Jr., EGGEN, D.A., McMURRY, M.T. On the association of cigarette smoking with coronary and aortic atherosclerosis. *Journal of Atherosclerosis Research* 10: 303–317, November-December 1969.

(76) THOMAS, W.A., JANAKIDEVI, K., REINER, J.M., LEE, K.T. Glucose-6-phosphate dehydrogenase (G-6-PD) monotypism in atherosclerotic lesions of heterozygotes related to lesion thickness. *Circulation* 54(4, Supplement II): 137, October 1976.

(77) TRACY, R.E., TOCA, V.T., STRONG, J.P., RICHARDS, M.L. Relationship of raised atherosclerotic lesions to fatty streaks in cigarette smokers. *Atherosclerosis* 38(3/4): 347–357, February-March 1981.

(78) TURNER, D.M. Carbon monoxide, tobacco smoking, and the pathogenesis of atherosclerosis. *Preventive Medicine* 8(3): 303–309, May 1979.

(79) U.S. PUBLIC HEALTH SERVICE. *Arteriosclerosis: Report by NHLI Task Force on Arteriosclerosis.* Volume 1. U.S. Department of Health, Education, and Welfare, Public Health Service. DHEW Publication No. (NIH)72–137, 1971.

(80) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM)71–7513, 1971, 458 pp.

(81) VIEL, B., DONOSO, S., SALCEDO, D. Coronary atherosclerosis in persons dying violently. *Archives of Internal Medicine* 122(2): 97–103, August 1968.

(*82*) VIKHERT, A.M., ZHDANOV, V.S., LIFSHITS, A.M. Atherosclerosis in males doing manual and brain work. *Kardiologija* 16(3): 119–123, 1976.

(*83*) VIKHERT, A.M., ZHDANOV, V.S., LIFSHITS, A.M. Influence of nutritional status and tobacco smoking on the development of atherosclerosis in male manual and brain workers. *Cor et Vasa* 18(3): 202–208, 1976.

(*84*) WENZEL, D.G., TURNER, J.A., KISSIL, D. Effect of nicotine on cholesterol-induced atherosclerosis in the rabbit. *Circulation Research* 7(2): 256–261, March 1959.

(*85*) WILENS, S.L., PLAIR, C.M. Cigarette smoking and arteriosclerosis. *Science* 138(3544): 975–977, November 30, 1962.

(*86*) WISSLER, R.W., GEER, J.C. (Editors). *The Pathogenesis of Atherosclerosis.* Baltimore, Williams & Wilkins Company, 1972, 262 pp.

(*87*) WORLD HEALTH ORGANIZATION. Atherosclerosis of the aorta and coronary arteries in five towns. *Bulletin of the World Health Organization* 53(5/6): 485–653, 1976.

SECTION 3. CORONARY HEART DISEASE

Introduction

Higher rates of disease and earlier mortality in cigarette smokers than in nonsmokers have been documented in a large number of investigations. Of the several disease manifestations that account for the excess disability and death in cigarette smokers, coronary heart disease (CHD) is the leading cause in North America and northern Europe (*18, 40, 43, 45, 67, 94, 96, 134, 143, 189, 214, 224, 257*). CHD is related to several risk factors, including cigarette smoking. Estimates indicate that up to 30 percent of all CHD deaths in the United States are attributable to the cigarette smoking habit (*189*).

Three of the major prospective studies have reported estimates of cigarette-related CHD mortality based on the number of observed versus expected CHD deaths in smokers and nonsmokers. In the ACS 25-State study, involving more than 1 million men and women, Garfinkel (*73*) estimated that of the 12,724 CHD deaths that occurred among all males followed prospectively for 6 years, 5,358 (46 percent) would not have occurred if all male cigarette smokers had the same CHD death rates as did nonsmoking males. Among females, a similar percentage of excess deaths (40 percent) attributed to smoking was noted; however the total number of CHD deaths was not large. Rogot and Murray (*224*) followed 290,000 U.S. veterans over a period of 16 years. During this time 13,845 CHD deaths were observed among cigarette smokers, whereas only 8,787 were expected. This represents an approximately 40 percent greater observed-to-expected ratio. In the British physicians study, in which 34,000 male British physicians were followed for 22 years, it was reported that cardiovascular disease accounted for 52 percent of all excess deaths in smokers, including 31 percent arising from CHD. By contrast, lung cancer was responsible for 19 percent of the cigarette-related excess deaths (*232*).

Whyte (*277*), using the "attributable fraction" method as advocated by Miettinan (*179*), reanalyzed data from the Pooling Project study and estimated that 24 percent of first major coronary events were cigarette related and independent of other risk factors. When all three major risk factors were considered together, the proportion of attributable risk increased to 70 percent.

Both Luce and Schweitzer (*163, 164*) and Boden (*21*) attributed 25 percent of all circulatory diseases to smoking. Both used data derived from estimates provided by the NIH Task Force Report on Preventive Medicine (*63*). These estimates are in close agreement with that published by Richter and Gori (*219*) that attributed 30 percent of heart disease to smoking; they also estimated that 33 percent of all arteriosclerosis was cigarette related. The latter estimate is identical to those published by the National Cancer Institute and the National Heart, Lung, and Blood Institute in the final report on the program to reduce the risk of disease in smokers (*189*).

In young people—including young women who are otherwise at very low risk for CHD—as many as three-quarters of the cases may be attributable to the cigarette smoking habit (*244, 257*). During the period 1965–1977, there were an estimated 2.8 million premature deaths from heart disease, primarily CHD, in American men and women attributable to the use of tobacco. Furthermore, unless smoking habits of Americans change, over 10 percent of all those now alive may die prematurely of heart disease that will be attributable to the use of tobacco. The number of such deaths may exceed 24 million (*189*).

Annually during recent years, more than one and a quarter million Americans have suffered fatal or nonfatal heart attacks (*2, 101, 198*). The deaths from CHD have numbered over 500,000 and have exceeded the deaths from any other cause; half or more of these deaths are sudden (*139*). In addition to these acute manifestations of CHD, more than 5 million Americans are under treatment for chronic manifestations of CHD (*2, 198*). Millions of others have significant CHD that is undiagnosed. Of those currently undiagnosed, approximately one-quarter will manifest sudden, unanticipated death as the first clinical indication of CHD (*110, 137, 153*).

Scientific Investigation of the Relationship Between Coronary Heart Disease and Smoking: Objectives of the Present Review

The scientific basis for the judgment that cigarette smoking is a major contributor to CHD in Americans has been presented in the Reports of the Surgeon General beginning in 1971 (*264*) and emphasized recently in the Reports of 1979 (*263*) and 1980 (*261*). A large number of epidemiologic, clinical, and experimental studies using a variety of methods and research designs have accumulated overwhelming evidence of the strong relationship between cigarette smoking and CHD. The possibilities of sample selection bias or confounding of this association by other factors as explanation for this association have been examined exhaustively and do not explain the relationship between cigarette smoking and CHD.

In this section, emphasis is placed on critical examination of the relationship between cigarette smoking and CHD incidence and mortality. The independence of cigarette smoking as a predictor of CHD is considered in the context of those other risk factors that also predict the occurrence of CHD. This includes evaluation of the consistency of the relationships between risk factors and subsequent CHD, including those mathematical models for prediction of CHD that have been applied widely among diverse population groups. The examination takes into account sample size, effects of multiple risk factors acting simultaneously, and secular trends in risk factor

prevalence. Areas of opportunity for expansion of knowledge are discussed.

Mortality studies are summarized with respect to the relationship of smoking and CHD. The large prospective mortality studies provide evidence of the influence of cigarette smoking in large and varied populations, and they provide sufficient numbers of cases for detailed analyses of the influence of smoking intensity and duration, age, sex, race, and smoking cessation on CHD.

Coronary Heart Disease Manifestations

The major clinical manifestations of CHD are myocardial infarction (MI), which may be fatal or nonfatal; other death from CHD, which may be sudden or not; and angina pectoris, which is the first clinical manifestation in about one-third of new cases (*40*).

In most cases, obstruction to blood flow in the coronary arteries is caused by arteriosclerotic narrowing (*34, 39*). Some cases are associated with coronary artery spasm with or occasionally without atherosclerotic change in the coronary arteries (*39, 87, 174, 202*). When there is thrombosis superimposed on the coronary narrowing, myocardial infarction typically results (*34*). The aggregation of platelets and formation of fibrin thrombi are related to the acute clinical manifestations of coronary heart disease, and may also play a role in the development of coronary atherosclerosis (*187, 230*). Several autopsy studies in the United States and elsewhere have shown that atherosclerosis of the coronary arteries is more common in cigarette smokers than in nonsmokers (*3, 7, 8, 9, 220, 245, 247*). This topic is discussed elsewhere in this Report.

Clinical Manifestations and Epidemiologic Criteria for Coronary Heart Disease Events

Myocardial Infarction

Myocardial infarction (MI) denotes necrosis of a discrete volume of heart muscle resulting from prolonged, severe ischemia following interruption of coronary blood flow. The characteristic symptom is unremitting chest pain that may be associated with sweating, nausea, shortness of breath, dizziness, or loss of consciousness. The role of coronary thrombosis in the evolution of acute myocardial infarction (AMI) has been debated in the past; recently, coronary angiography has been performed in large numbers of patients with AMI. In the majority, coronary thrombosis has been found to be superimposed upon preexisting arteriosclerotic narrowing. In a small proportion of cases, but more commonly in young men and women, MI has been observed in patients with little or no coronary

atherosclerosis who have had coronary artery spasm or coronary thrombosis or both (*1*).

Loss of consciousness in acute myocardial infarction is an ominous sign because it often reflects inadequate pumping action of the heart owing either to catastrophically abnormal cardiac rhythm or to severe deterioration of cardiac muscle function. A broad range of cardiac rhythm disturbances may occur, but the most characteristic catastrophic one accompanying myocardial infarction is a chaotic irregularity of muscle fiber contraction (ventricular fibrillation) that results in a cessation of effective pumping by the heart. In such instances, death occurs within several minutes after cessation of blood flow to the brain if the rhythm disturbance is not reversed.

In patients who survive long enough to be admitted to the hospital, the diagnosis of AMI may be made from changes in the electrocardiogram and increases in serum enzymes (*1*). In comprehensive clinical epidemiologic studies, the criteria for identifying cases of MI include specific presenting symptoms, electrocardiographic changes, and serum enzyme elevations (*40, 214*).

Death from CHD

In fatal cases, evidence of CHD may be provided by clinical or autopsy information (*40, 214*). In the absence of adequate clinical or autopsy evidence, diagnosis of death from CHD is based on documentation of a sufficiently short interval from onset of symptoms until death and the absence of another potentially lethal condition (*153*).

Sudden Cardiac Death

A large proportion of deaths certified as due to CHD have been sudden, and a significant fraction of these sudden cardiac deaths (SCD) have occurred in persons with no prior history of CHD (*68, 109, 139, 152, 154, 220*). The incidence of SCD increases with age, and it is substantially more frequent in men than in women; in women the incidence of SCD lags behind that of men by 20 years (*139*).

Epidemiologic investigations have shown that the majority of deaths in ambulatory adults that are sudden and unanticipated are associated with severe CHD. In the Baltimore study by Kuller et al. (*153*), 71 percent of the deaths (excluding trauma) that occurred within 24 hours of the onset of terminal illness in individuals who had been able to function in the community were from CHD. In those with other causes, more than half were associated with fatty liver. Alcohol consumption appears to have a complex relationship to CHD, and heavy alcohol consumption has been identified as a factor in sudden death in several studies. This relationship has been shown to be independent of the relationship with cigarette smoking (*38, 64, 148, 158, 173, 188, 209, 216*). Although some difficulty may arise in

appropriate designation of unwitnessed deaths, the less frequent and rare conditions are usually differentiated easily from SCD.

Criteria for SCD have varied in different studies. Among ambulatory adults considered to be well who die suddenly, the probability of severe CHD has been shown to be very high both by autopsy data and by clinical data (*40, 109, 139, 157, 200, 248*). In large population studies, however, information for some cases is often not available to determine the exact interval from onset of symptoms until death; therefore, criteria for sudden death have often included intervals up to 24 hours (*153, 156, 200*). In a high proportion of such cases, severe CHD has been observed by autopsy examination (*10, 12, 50, 68, 109, 153, 160, 200, 208*).

The physiologic disorders responsible for sudden collapse and cardiac arrest in ambulatory adults have been well documented. In the overwhelming fraction, ventricular fibrillation is the terminal ventricular rhythm disorder; however, profound cardiac bradycardia or cardiac standstill can be the mechanism as well. Ventricular fibrillation may further degenerate into cardiac standstill (*33, 47, 55, 56, 145, 202*). Among patients resuscitated following cardiac arrest, AMI has been documented during the subsequent hospital course in one-quarter to one-half of the cases; in the others, severe, multivessel coronary atherosclerosis, with or without old MI, has been observed by coronary angiography in three-quarters or more (*33, 56, 273*).

Ascertainment of CHD From Death Certificates

In large-scale mortality studies the underlying cause of death on death certificates has usually been used to identify the deaths from coronary heart disease. [In recent editions of the *International Classification of Diseases,* the term ischemic heart disease is preferred over the older term coronary heart disease. Some authors prefer the term arteriosclerotic heart disease. For uniformity, coronary heart disease (CHD) is used throughout this section regardless of the usage in the publications reviewed.] The accuracy of death certificate data has been evaluated through review of available clinical data and retrospective analyses and from available pathological data. Coronary heart disease has been confirmed as probable or likely in the vast majority of cases (*183, 184, 236, 284*).

In a random sample of 1,362 U.S. death certificates in 1960, pertinent clinical and pathological information to determine the cause of death was investigated by Moriyama et al. (*182*). In the 87 percent of cases for which responses from medical certifiers were obtained, only 7 percent of those certified to be CHD were judged to be incorrect or probably incorrect. The information for diagnosis of CHD was judged to be reasonable or well established in 74 percent and inadequate to determine the cause of death in 19 percent.

In recent years, cardiac evaluation has become more prevalent with widespread use of objective diagnostic tests. This should result in even greater accuracy of CHD case ascertainment from death certificates.

Angina Pectoris

Angina pectoris is the first clinical manifestation in about one-third of the new cases of CHD (*133*). In the typical form, observed in about 90 percent of clinically diagnosed patients, chest pain or tightness occurs with exertion or excitement and is relieved promptly by rest or nitroglycerin. Such patients usually have fixed obstruction to blood flow due to arteriosclerosis in one or more of the coronary arteries (*34, 174, 237*). Patients with typical angina pectoris are at increased risk for the more serious manifestations of CHD, myocardial infarction, and death from CHD (*34, 133, 174, 175, 241*).

In the atypical form, chest discomfort usually occurs at rest, although it may also occur with exertion, and it is usually relieved by nitroglycerin (*87, 174, 175, 237, 241*). This atypical or variant form of angina pectoris has been shown to result from coronary artery spasm that occurs at the site of atherosclerosis in many cases, but in otherwise normal-appearing coronary arteries in others (*87, 175, 202*). Sudden death is a rather common complication of variant angina (*39, 110, 175, 202, 241*).

Conditions other than CHD may cause symptoms that mimic angina pectoris, and definitive diagnosis may require clinical observation over time and the performance of ancillary diagnostic procedures (*34, 40*). However, in large-scale epidemiologic studies, complete diagnostic evaluation is usually not feasible, and the proportion of cases with underlying severe coronary atherosclerosis has probably varied among the different studies (*40, 121, 273*).

In addition to those in the population who have symptoms of CHD, there are many with significant coronary atherosclerotic obstruction who are undiagnosed. The frequency of clinically silent but physiologically significant coronary artery disease is unknown; it is estimated that in one-quarter of the cases with a new myocardial infarction, the infarction is silent and detected only on followup by electrocardiographic (ECG) examination (*172*).

In prospective epidemiologic studies with clinical followup, cases may be classified only by the most severe CHD manifestation, in this order: death from CHD, nonfatal myocardial infarction, and angina pectoris. Thus, the cases classified as angina pectoris are those remaining who have not experienced a more serious CHD event, and as noted above, this diagnosis may lack sensitivity and specificity for coronary atherosclerotic disease. Variation in the strength of association between smoking and angina pectoris may be influenced by these methodological considerations (*48, 49, 121, 135, 229*).

A number of well-documented, clinical series of patients with angina pectoris and severe CHD confirmed by coronary angiography, surgery, or post-mortem examination have been reported (*4, 11, 32, 42, 97, 98, 118, 171, 201, 253, 268, 272*). These studies provide important information for clinical management and add insights into relationships with risk factors. However, causal inferences must be made with caution when measurements of risk factors have been made after the onset of clinical disease and data from appropriate comparison groups are not available.

Epidemic CHD and the Application of Epidemiologic Methodology

CHD was thought to be uncommon in the early part of this century when most deaths were caused by infectious disease. Before the mid-century, however, CHD had become the leading cause of death, and year to year increases were large (*101, 159*). Neither the cause of CHD nor the reasons for the rising epidemic could be explained. Nevertheless, pioneering efforts in cardiovascular epidemiology revealed that certain characteristics were observed more often in CHD cases, and epidemiologic investigations were begun to obtain data with which to make causal inferences (*40, 86, 143*).

Prospective Cohort Studies: Intensive Population Studies of Risk Factors and CHD

In several early investigations, cigarette smoking and several other characteristics were observed to be strongly associated with CHD (*60, 136, 276*). To clarify the nature of these relationships, defined population samples were examined for personal characteristics that could be related to CHD. Intensive observation for subsequent incidence of CHD through reexamination and surveillance activities in members of population samples that were free of disease at the baseline examination provided a substantial part of the data from which causal inferences relating to smoking and CHD were made. A number of these are briefly described in the following pages. In each study, smokers were found more likely to develop CHD than nonsmokers.

Studies in U.S. Whites

Within the U.S. population, CHD mortality has been highest in white men, and they were investigated most intensively in the early prospective studies. To provide a sufficiently large number of cases for detailed analyses of the relationship of CHD to cigarette smoking and other risk factors, several of the long-term epidemiologic studies agreed to pool their data in the National Cooperative Pooling Project

sponsored by the Council on Epidemiology of the American Heart Association and supported by the American Heart Association and the National Heart Institute, now designated the National Heart, Lung, and Blood Institute (*168, 214*). Five of the studies participating in this effort had used comparable methodology in data collection so that the data from each of these five cohorts could be pooled for analysis. In Table 1, analyses for the pooled data are referred to as "Pool 5." The five cohort studies contributing to the pooled data will be characterized briefly individually, and then analysis of the pooled data will be summarized.

Framingham Heart Disease Epidemiology Study

The Framingham study was initiated by the Public Health Service in 1948. The members of the prospective cohort were 2,282 men and 2,845 women who were aged 29 through 62 and free of CHD at initial examination (*40, 86, 133*). The cohort was based on a random subsample of the residents of Framingham, Massachusetts; the response rate was 69 percent. The respondents were supplemented by volunteers who had similar characteristics. A standardized cardiovascular examination at entry included information on habits, physical characteristics, and blood chemistries. Reexamination has been carried out biennially for ascertainment of cardiovascular disease and changes in characteristics. Cardiovascular disease case ascertainment has included community and mortality surveillance activities (*86, 136*). Analyses through 24 years of followup have shown that cigarette smoking is strongly related to MI and death from CHD (*40, 133, 135*). In Table 1, Framingham data analysis is shown with that of the other cohorts participating in the National Cooperative Pooling Project. The excess risk of MI and death from CHD was found to increase progressively with the number of cigarettes smoked (Table 1).

The relationship to angina pectoris has been less clear. In the 12-year and the 24-year followup data analyses, however, male cigarette smokers were observed to experience a higher incidence of angina pectoris than were nonsmokers (*40, 135*). The effect was stronger at younger ages; after 24 years of followup, the incidence of angina pectoris in those 30 to 39 years old at entry to the study was twice as high in smokers as in nonsmokers (Figure 1).

Albany Cardiovascular Health Center Study

In 1952 the New York State Health Department established at the Albany Medical College a prospective study of male civil servants working in Albany. Participation was obtained from 87 percent of eligible men aged 40 through 54, of whom 1,823 were free of CHD at initial examination. After 6 years, the incidence of MI and death from CHD was significantly higher in cigarette smokers in compari-

TABLE 1.—National Cooperative Pooling Project. Analysis of the incidence of CHD by smoking behavior in five participating cohorts individually and in the data pooled for the five cohorts with comparable methodology (Pool 5). Standardized incidence ratio, risk ratios, number of men, person-years of experience, and number of first events

Smoking behavior	Standardized incidence ratio by study group					
	Pool 5	ALB	CH-GAS	CH-WE	FRAM	TECUM
All	100	100	100	100	100	100
Nonsmokers	58	55	48	59	67	(53)
Never smoked	54	45	(53)	44	77	(60)
Past smoker	63	67	56	89	(46)	(50)
<1/2 pack/day	55	(67)		(43)	78	(43)
Cigar and pipe only	71	78	(58)	98	57	(61)
Cigarette smokers						
About 1/2 pack/day	104	(52)	(64)	139	106	(151)
About 1 pack/day	120	108	125	128	119	117
>1 pack/day	183	200	190	162	174	151
Risk ratio ≥1 pack/day Nonsmokers	2.5	2.7	3.3	2.4	2.2	( )
95% confidence interval						
Low	2.1	1.8	2.1	1.6	1.5	( )
High	3.1	4.3	6.2	3.7	3.4	( )
Risk ratio >1 pack/day Nonsmokers	3.2	3.7	4.0	2.8	2.6	( )
95% confidence interval						
Low	2.6	2.4	2.5	1.2	1.8	( )
High	4.2	6.1	8.4	5.5	4.5	( )
Number of men at risk	8,282	1,796	1,258	1,926	2,162	1,140
Person-years of experience	70,970	17,240	11,017	16,072	19,756	6,885
Number of first events	644	154	123	140	178	49

NOTE: ALB: Albany Cardiovascular Health Center Study
CH-GAS: Chicago Peoples Gas Company Study
CH-WE: Chicago Western Electric Company Study
FRAM: Framingham Heart Disease Epidemiology Study
TECUM: Tecumseh Health Study
NOTE: ( ): based on fewer than 10 first events.
SOURCE: Pooling Project Research Group (*214*).

son with nonsmokers (*48*). Subsequent analysis after 10 years of followup confirmed these findings (Table 1).

Chicago Peoples Gas Company Study

Beginning in 1958, the Chicago Peoples Gas Company medical department examined 1,264 white men aged 40 to 59 (92 percent of

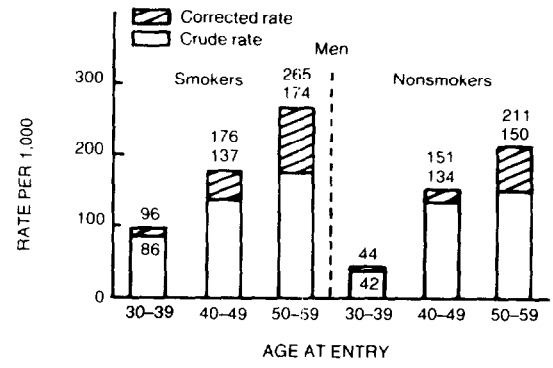


FIGURE 1.—Twenty-four-year incidence of angina pectoris in men, by cigarette smoking status

NOTE: The crude rates have been corrected to take into account those members of the population who are no longer at risk by reason of having developed the disorder in question or having been lost to observation by death.
SOURCE: Dawber (*40*).

those eligible) who were free of CHD (*161, 214*). Analysis of the data obtained during an average of 8.8 years of followup revealed a higher incidence of MI and death from CHD in cigarette smokers than in nonsmokers (Table 1).

Chicago Western Electric Company Study

Beginning in 1957, 67 percent of male Western Electric Company, Chicago, employees aged 40 to 55 were examined; 1,981 were free of CHD (*161, 206, 214*). After an average followup of 8.3 years, the incidence of MI and death from CHD was higher in cigarette smokers than in nonsmokers (Table 1).

Tecumseh Health Study

The Tecumseh health study began examination of the entire community of Tecumseh, Michigan, in 1959; participation was obtained from 90 percent (*61, 214*). Included was a cohort of 1,240 white men aged 40 to 59 who were free of CHD at initial examination. During an average followup of 8.05 years, the incidence of MI and death from CHD was higher in cigarette smokers than in nonsmokers (Table 1).

Minnesota Business and Professional Men Study

Selected Minnesota business and professional men were first examined in 1948; 284 men aged 40 to 59 years were free of CHD (*144, 214*). During an average followup of 14.1 years, those who

smoked cigarettes experienced a higher incidence of MI and death from CHD than did nonsmokers.

Minnesota-Based Railroad Worker Study

Among eligible railroad men working in the northwest sector of the United States, 65 percent participated in the Minnesota-based railroad worker study examinations beginning in 1958 (*143, 214*). Of these men, who were white, aged 40 to 59 years, and free of CHD at first examination, 2,571 were followed for an average of 4.9 years. Those who smoked cigarettes experienced a higher incidence of MI and death from CHD than did nonsmokers.

National Cooperative Pooling Project

As indicated above, the data from five of the cohorts participating in the National Cooperative Pooling Project were pooled for those white men who were aged 40 to 59 years, were free of CHD at initial exam, had comparable baseline examinations, and were followed for up to 10 years with comparable case ascertainment (Table 1). The demographic and other characteristics of these cohorts were similar to the characteristics of middle-aged white men in general living in the United States during the same period (*190–196*).

Subjects contributing to the pooled data numbered 8,422; during an average followup of 8.5 years (72,011 person-years), 688 cases of major CHD were observed (*214*). Major CHD was defined as nonfatal or fatal MI or sudden death from CHD (death in less than 3 hours from the onset of illness).

Risk of CHD With Smoking

According to the pooled data for men aged 40 to 59, those who smoked a pack or more of cigarettes per day at initial examination experienced a risk for a first major coronary event that was 2.5 times as great as the risk of nonsmokers (Table 1). In these analyses, nonsmokers included those who never smoked, cigar and pipe only smokers, past smokers, and those who smoked less than half a pack per day. Those smoking less than half a pack per day consisted largely of those who smoked occasionally or only two or three cigarettes per day. For each of the five cohorts separately, the relative risks varied from 2.2 to 3.3.

The risk was greatest in those with the heaviest smoking habits in all age groups (Table 2), and excess incidence attributable to smoking more than one pack of cigarettes per day tended to increase with increasing age up to age 60; however, with increasing age, relative risk declined. This apparent paradox is due to the rapid rise of CHD incidence with age. The excess incidence in heavy smokers (more than one pack per day) was large and statistically significant for

TABLE 2.—National Cooperative Pooling Project. Analysis of the risk of CHD by smoking behavior from the pooled data of the five cohorts* observed with comparable methodology (Pool 5). Average annual risk of first major coronary event, standardized incidence ratio (SIR), risk ratio >1 pack per day/nonsmokers, and number of first events, by age group

Smoking pattern	Age group					
	40–44	45–49	50–54	55–59	60–64	40–64
	Average annual risk (per 1,000 man-years)					SIR
All	3.1	6.4	8.0	22.6	19.9	100
Nonsmoker	(1.5)	3.0	3.6	7.3	15.5	58
Never smoked	(1.9)	(0.7)	(2.5)	8.7	11.4	54
Past smoker	(0.9)	5.5	4.3	6.1	15.5	63
<1/2 pack/day	(1.7)	(4.7)	(5.9)	(6.4)	(7.5)	55
Cigar and pipe only	(2.1)	(2.2)	(2.1)	12.1	19.5	71
Cigarette smokers						
About 1/2 pack/day	(3.1)	(5.0)	(6.2)	15.5	24.3	104
About 1 pack/day	3.9	8.4	10.3	13.8	22.0	120
>1 pack/day	4.9	12.2	17.4	22.5	26.8	183
Risk ratio						
> pack/day/nonsmokers	( )	4.1	4.8	3.1	1.7	3.2[1]
	Number of first events					SIR
All	34	113	158	194	145	644
Never smoked	3	2	8	21	21	55
Past smoker	1	11	10	13	18	53
<1/2 pack/day	1	4	6	6	4	21
Cigar and pipe only	2	4	5	26	33	60
About 1/2 pack/day	3	7	9	19	15	53
About 1 pack/day	14	49	64	61	42	230
>1 pack/day	10	36	56	48	22	172

* See footnote of Table 1 for names of the five study groups.
[1] Approximate 95% confidence interval: 2.6–4.2.
NOTE: ( ): based on fewer than 10 first events.
SOURCE: Pooling Project Research Group (*214*).

each 5-year age group between 45 and 64, and the differences were progressively greater with age up to 60. For those smoking about one pack per day and about one-half pack per day, the excess risks were sizable, but of a lower magnitude. Because of the relatively smaller numbers, the data were not sufficient for evaluation of differences in risks among those who had never smoked, those who had smoked less than one-half pack per day, and former smokers.

In the Pooling Project data, the risk for cigar and pipe smokers was not significantly different from either the nonsmoker group or

the half-pack per day smokers, but it was significantly lower than that for men who smoked a pack of cigarettes per day (Table 2). However, the position of cigar and pipe smokers on the continuum of risk could not be adequately evaluated from these data because of small numbers.

In summary, detailed prospective studies of the incidence of CHD in white males in the U.S. population have demonstrated a clear, strong, dose-related relationship between cigarette smoking and acute myocardial infarction and death from CHD. This cigarette smoking effect was proportionally greater in younger populations, but was present in all age groups examined in these studies. Cigarette smokers in the Framingham study had a high incidence of angina pectoris among the younger age groups, but this relationship was not as strong as the relationship between smoking and myocardial infarction. Pipe and cigar smokers had a risk that was not statistically different from the risk of nonsmokers.

Ethnic Groups in the United States With Lower Risk of CHD

CHD mortality in blacks is lower than in whites in the United States (*75, 76, 197, 225, 236, 259*). A case–control study of the incidence of CHD during World War II in young Army men observed a risk ratio of 0.61 in black men relative to white men (*120*). Reasons for lower rates in black men are not adequately understood, although the smoking habits of blacks have been found to differ from those of whites. Blacks have tended to smoke cigarettes with higher tar and nicotine content, but they have also tended to smoke fewer cigarettes (*262*). Hypertension is also more prevalent in blacks than in whites (*142*). On the other hand, plasma lipid levels were reported to be more favorable; high density lipoprotein cholesterol levels (HDL-C) were higher and low density lipoprotein cholesterol levels (LDL-C) were lower in black men than in white men aged 20 to 49 (*259*). HDL-C has been negatively associated with CHD, and LDL-C has been positively associated with CHD (*80, 84, 217*).

The Evans County, Georgia, study was initiated in 1960 to investigate differences in coronary heart disease incidence and risk between blacks and whites for an entire community in a rural, principally agricultural setting (*107*). All residents of Evans County over age 40 and a 50 percent subsample of those aged 15 to 39 years were eligible; 92 percent of those eligible were examined between 1960 and 1962. Followup examinations from 1967 through 1969 provided a mean followup period of 7 1/4 years. Reexamination for evidence of new CHD was obtained in 91 percent of the 3,102 initially examined members of the population, including 537 black males and 947 white males (83 percent and 93 percent, respectively, of those initially available). In addition, community and mortality

surveillance was used to ascertain the incidence cases of fatal and nonfatal CHD.

During the 7 1/4 years of followup, 13.6 percent of the black males and 12.7 percent of the white males died. The onset of CHD was observed in 6 surviving and 7 decedent black men and in 40 surviving and 32 decedent white men. The age-adjusted incidence rate for white men was 3.5 times the rate in black men. There were few cases in women, but the incidence rates in black women and in white women appeared to be similar. CHD incidence was higher in smokers than in nonsmokers for the black and the white populations.

Beginning in 1965, 9,824 men aged 45 to 64 years who were residents of four rural and three urban areas of Puerto Rico were examined at a clinic in San Juan. The methods used were comparable to those used by the Framingham study (*85*). Of the targeted population samples, over 80 percent attended the medical examination, and over 90 percent of the examined cohort participated in four followup examinations at 2 1/2-year to 3-year intervals. The average followup was 8 1/4 years (*246*).

In comparison with men in Framingham, fewer men in Puerto Rico were smokers, and the Puerto Rican smokers consumed fewer cigarettes per day (*85*). After 2 1/2 years of observation, the incidence of CHD in Puerto Rican men was only half that observed in Framingham, and the difference between smokers and nonsmokers was not significant (*222*). However, after 8 1/4 years of observation and the accumulation of approximately four times as many cases, cigarette smokers had a significantly higher incidence of MI than did nonsmokers; this was true both for those living in the rural areas and for those in the urban areas when considered separately (*246*).

Japanese Americans have an incidence and mortality from CHD that is intermediate between the very low rates in Japan and the high rates in white Americans (*83, 222, 284*). The explanation for this gradient of CHD with migration has been investigated by the Ni-Hon-San study centering on a cohort of Japanese Americans living in Hawaii (*14, 221*).

The target cohort of the Honolulu heart study was all noninstitutionalized men of Japanese ancestry born between 1900 and 1919 who were living on the Island of Oahu in 1965 (*130*). Initial examinations were conducted between 1965 and 1968, and participation was obtained from 72 percent of the identified men who were eligible (7,705 men aged 45–69 years and free of CHD). CHD incidence was observed by followup examination (at 2 and 6 years) and by intensive community and mortality surveillance activities. The 2-year incidence of MI and death from CHD was only half of that observed in Framingham men, but was significantly higher in

cigarette smokers (*85*). The relative risk for those smoking 21 or more cigarettes per day was six times higher than for nonsmokers (*221*). At 6 years of followup, the risk of MI and death from CHD, but not of angina pectoris, was strongly related to cigarette smoking, and the risk increased in proportion to the number of cigarettes smoked per day (*130*).

CHD death rates are lower in Great Britain than in the United States by about one-fourth, and those in Norway are substantially lower than either. In 1962 the National Heart Institute and the National Cancer Institute in the United States, the London School of Hygiene and Tropical Medicine, and the Norwegian Cancer Registry undertook a study to examine differences in death rates among migrant populations to the United States (*223*). Native-born Americans were included in the study for comparison. Approximately 32,000 British migrants and 18,000 Norwegian migrants aged 30 to 74, residing in 12 States, were sent questionnaires. For native-born Americans, similar questionnaires were sent to a subsample of 23,000 white persons drawn from a 1961 National Health Survey sample covering the same geographic areas. A total of 7,895 CHD deaths occurred (3,193 British, 1,213 Norwegian, and 3,489 native-born deaths). Norwegian migrants exhibited the lowest CHD death rates. British migrants' rates were about equal to those for native-born Americans.

The decedent's cigarette smoking status as of October 1962 was requested from the next of kin. Smoking status from October to the end of the study period (1963–1966) was presumed not to be altered. Mortality ratios for CHD were significantly elevated among smokers compared with nonsmokers, particularly at the younger ages. The ratios were 1.9 or greater for both males and females at age 45 to 54 years and decreased somewhat with age. CHD death rates among smokers demonstrated little difference between the three groups, and ratios were greater for female than male smokers in all but two instances. Table 3 provides a summary of these mortality ratios by migrant class, age, and sex.

In summary, a number of ethnic groups in the United States have lower rates of CHD, but even in these populations, the risk of MI and CHD death are significantly higher in smokers than in nonsmokers.

Studies in Other Countries

Cigarette smoking has been found to be related to the incidence of CHD in other countries where long-term followup of large, defined cohorts has been performed. For some cohorts, early data analyses with relatively few cases have not shown significant differences, but later followup analyses with large numbers of cases have usually demonstrated a positive relationship between cigarette smoking and CHD.

TABLE 3.—Coronary heart disease mortality ratios (smoker versus nonsmoker) of British and Norwegian migrants to the United States and native-born Americans by age, sex, and cigarette smoking status

Group	Age and mortality ratio (smoker vs. nonsmoker)		
	45–54	55–64	65–74
British migrants			
Males	1.9	1.3	1.3
Females	2.9	2.4	1.7
Norwegian migrants			
Males	2.3	1.5	1.6
Females	—[1]	2.3	2.0
Native-born Americans			
Males	2.3	2.7	1.4
Females	2.8	2.0	1.3

NOTE: All nonsmoker ratios are 1.0.
[1] Less than 10 deaths.
SOURCE: Rogot (*223*).

An international study conducted in seven countries observed large differences in CHD incidence and mortality among 16 cohorts of men aged 40 to 59 at baseline examination in the United States, Europe, and Japan (*143*). The United States cohort was the railroad men described above in the Pooling Project (*214*). This cohort experienced a relative risk of CHD with cigarette smoking that was similar to that of other U.S. cohorts of white men (Table 1). The other cohorts of men were residents of Yugoslavia (Dalmatia, Slovenia, Velika Krsna, Zrenjanin, and Belgrade), Japan (Ushibuka and Tanushimaru), Finland (districts in the east and west), Italy (Crevalcore, Montegiorgio, and railroad men in Rome), the Netherlands (Zutphen), and Greece (Crete and Corfu). In all, 12,763 men were examined, of whom 12,509 were free of evidence of coronary heart disease at baseline examination. During the 10 years of followup, 1,512 deaths occurred from all causes, and 413 were attributed to coronary heart disease.

Ten-year CHD death rates were less than 75 per 10,000 for the cohorts living in Crete (Greece) and in Croatia (Yugoslavia) and for the two cohorts in Japan; however, for the cohorts of east and west Finland, the U.S. railroad men, Zutphen (the Netherlands), and Belgrade (Yugoslavia), the CHD death rates were 250 per 10,000 or higher. Although the cohorts participating in the Seven Countries study were not selected as representative of their countries, the CHD death rates of cohorts grouped by country were highly correlated

with the CHD death rates for men of the same ages reported in the vital statistics of these countries.

Cigarette smoking was strongly related to CHD mortality in those cohorts with both high CHD death rates and relatively large numbers of cases for analysis. For example, among U.S. railroad men, CHD death rates were about three times as high in men who smoked 20 or more cigarettes per day compared with men who had never smoked or men who had stopped smoking. Furthermore, the association between CHD and number of cigarettes smoked daily was stronger in the cohorts with high CHD mortality than in the cohorts with low CHD mortality. Among northern European men as well as United States railroad men, the 10-year age-standardized CHD death rates increased significantly with the level of cigarette smoking, and the risk for northern European men smoking 20 or more cigarettes per day was more than four times greater than for men who had never smoked (Figure 2). For the southern Europeans, however, differences were only twofold and not statistically significant. Age-standardized rates for death from all causes, respiratory tract cancer, and neoplasms were also more closely related to the number of cigarettes consumed in northern Europe than in southern Europe, and for all deaths the differences were significant in both regions.

The 10-year incidence data provide a larger number of cases for analysis, as deaths from CHD represented only about 20 percent of the total CHD incidence in the Japanese and European cohorts. Definite CHD was observed in 351 of the 9,780 men during the followup period. The highest rate (11 percent) was observed in east Finland, and the lowest (0.3 percent) was observed in Crete (Table 4). Rates within countries were similar in general, but in Greece the rates were higher in Corfu than in Crete; in Finland the rate in the eastern district was double that in the western district; in Yugoslavia, the Serbian cohorts in Belgrade and Zrenjanin were similar, but in the farming village of Velika Krsna the rate was only half as high. The Japanese cohorts were small and the incidence too low for evaluation of the influence of smoking. Only 19 men in the two Japanese cohorts were observed to develop definite coronary heart disease during the 10 years of followup.

To provide greater stability in analyses, the European cohorts were grouped together by region: the three cohorts in Finland and the Netherlands, the five cohorts in Yugoslavia, and the three Italian cohorts with the two Greek cohorts. The 10-year CHD incidence in Finland and the Netherlands was significantly related to the number of cigarettes currently smoked, and former smokers had a CHD incidence that was twice that of those who had never smoked (Figure 3). In Yugoslavia, the CHD incidence in smokers was nearly twice that of those who had never smoked. Also in Yugoslavia, the CHD incidence was nearly three times higher for those

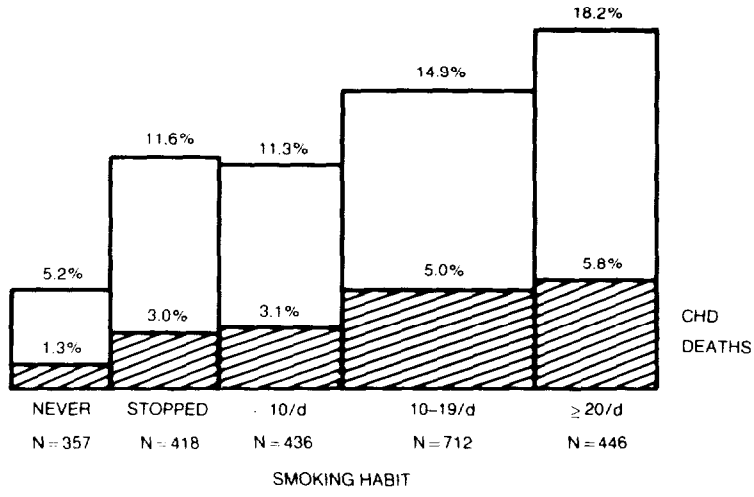


FIGURE 2.—Age-standardized 10-year death rates from all causes and from coronary heart disease of men in northern Europe (east and west Finland and Zutphen), classified by smoking habit at entry; all free of cardiovascular disease at entry

SOURCE: Keys (*143*).

smoking 20 or more cigarettes per day at entry compared with those who had never smoked, but no significant differences were observed between former smokers and never smokers (Figure 4). In the Italian and the Greek cohorts, the contrasts were less marked (Figure 5). The incidence of CHD was significantly higher in those northern Europeans and Yugoslavs smoking 10 or more cigarettes per day compared with lighter smokers, never smokers, or ex-smokers. The rates were also higher in the Italian and Greek cohorts, but were not statistically significant.

Observation of the Italian cohorts has continued, and 20-year followup data were recently reported (*126*). With the substantially larger number of cases, a significantly higher incidence of CHD was observed in cigarette smokers than in nonsmokers. The 20-year incidence of CHD increased from 90 per 1,000 in those who had never smoked to 159 per 1,000 in those smoking 10 to 19 cigarettes per day. The incidence in the highest smoking category (20+ cigarettes per day) was slightly lower (140 per 1,000) than the rate in those smoking from 10 to 19 cigarettes per day.

A number of prospective studies of CHD have been performed in the United Kingdom. Those with mortality followup—for example,

TABLE 4.—Ten-year incidence of coronary heart disease among men free of cardiovascular disease at entry (age-standardized rate per 10,000)

Cohort	N	Hard CHD			Any CHD		
		N	Rate	SE	N	Rate	SE
Dalmatia	662	13	185	52	40	629	94
Slavonia	680	18	253	60	40	561	88
Tanushimaru	504	8	148	54	20	354	82
East Finland	728	71	1,074	115	201	2,868	168
West Finland	806	45	539	80	129	1,582	129
Crevalcore	956	43	450	67	105	1,080	100
Montegiorgio	708	22	353	69	64	966	111
Zutphen	845	45	513	76	91	1,066	106
Ushibuka	496	11	204	63	23	458	94
Crete	655	2	26	20	13	210	56
Corfu	525	17	337	79	37	686	110
Rome railroad	736	25	357	68	57	786	99
Velika Krsna	487	6	132	52	21	452	94
Zrenjanin	476	12	239	70	37	715	118
Total	9,780	351	369.9[1]	19.1	913	943.8[1]	29.6

[1] Mean of the cohort rates weighted by the number at risk in each cohort.
SOURCE: Keys (*143*).

the British physicians study and the Whitehall study—are reviewed below under the heading Prospective Mortality Studies.

Morris and Kagan and associates (*185*) investigated differences in CHD in drivers and conductors working on London buses. Among other positive associations, those who smoked were found to have a higher 5-year incidence of CHD than those who did not smoke.

In 1977 Morris, Marr, and Clayton (*186*) reported followup on workers who were 30 to 67 years of age at examination. The sample was of 337 men living in London and in southeast England who had participated in a 7-day individual dietary survey. By 1976, 45 of these men had developed clinical CHD. Among the CHD cases, cigarette smoking was significantly more frequent than expected, and this was true for each occupational group: bank staff, bus drivers, and bus conductors. Estimated relative risks (compared with nonsmokers) were 3.5 for those smoking 11 to 20 cigarettes and 4.7 for those smoking more than 20 cigarettes (*88*).

The Belfast practitioner's study was initiated in 1964, using experienced, self-selected practitioners to observe the operation of risk factors in middle-aged men who were community residents (*88*). The sample comprised all men born in the 10-year period 1909–1918 (age 45 to 54 at the beginning of the study) who were registered in six cooperating group practices. Examinations were performed in 69 percent of the designated population sample. Among the 1,202 subjects free of CHD at the initial examination, 104 developed CHD

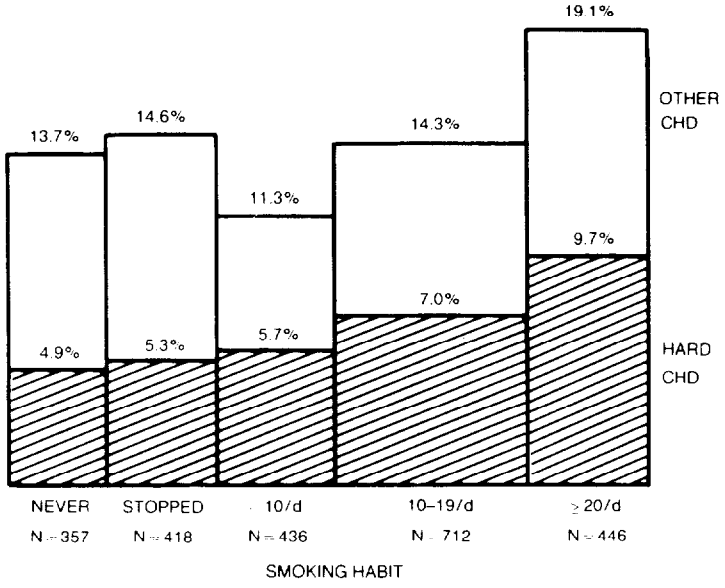


FIGURE 3.—Age-standardized 10-year incidence rate of coronary heart disease of 2,369 men in northern Europe (east and west Finland and Zutphen), classified by smoking habit at entry and then free of cardiovascular disease

SOURCE: Keys (*143*).

during the 5-year period of followup. MI occurred in 55 (15 fatal), cardiac ischemia in 5, and angina pectoris in 49. Current tobacco consumption, total years of smoking, and total tobacco consumption were significantly higher in the cases with CHD than in the overall population sample.

The Stockholm prospective study examined and followed men and women attending a health survey center in 1961 and 1962 (*26*). This sample was not a randomly selected population sample of Stockholm, but the incidence of myocardial infarction was similar to that of the Stockholm county population (*27*). A principal objective was to examine the relationships of fasting plasma triglyceride and cholesterol values to the future development of CHD. In analysis of 9-year followup data for 3,168 men, the incidence of MI and death from CHD with all ages combined was about fourfold higher for smokers than for nonsmokers (*26*). The difference was statistically significant. Risk factors for MI were evaluated in 3,189 men, among whom 130 experienced myocardial infarction during 14 years of followup; cigarette smokers experienced nearly three times the incidence of

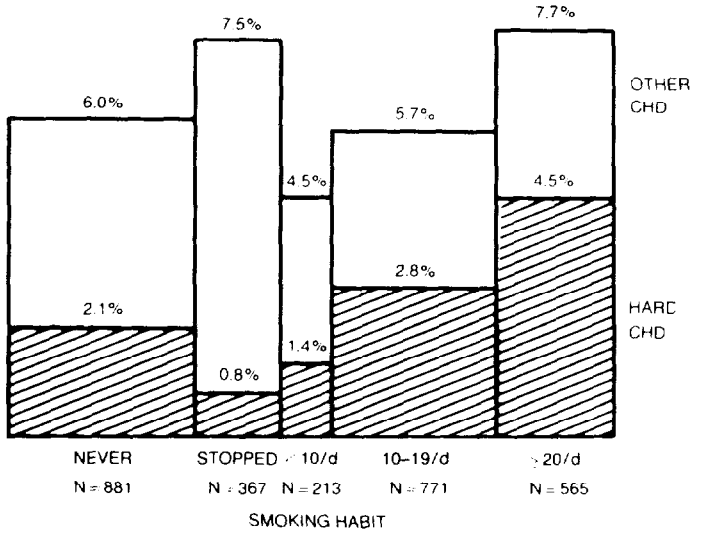


FIGURE 4.—Age-standardized 10-year incidence rate of coronary heart disease of 2,797 men in Yugoslavia (Dalmatia, Slavonia, Velika Krsna, Zrenjanin, and Belgrade), classified by smoking habit at entry and then free of cardiovascular disease

SOURCE: Keys (*143*).

MI experienced by nonsmokers (*27*). In analysis of risk factors and death during 14.5 years of followup of 3,486 men and 2,738 women, death due to ischemic vascular disease (principally CHD and stroke) was significantly related to smoking in men and in women (*22*).

The Section for Preventive Medicine at the University of Göteborg has observed the relationship of smoking and other risk factors to the incidence and the mortality from CHD in several studies of the Göteborg population (*278*). In 1963 a 30 percent sample of men born in 1913 was examined (at age 50) and followed; 88 percent participation was obtained, and 834 were found to be free of CHD. In 1970 a primary prevention trial was begun for examination of 10,000 intervention and 20,000 control subjects 47 to 54 years of age.

The 1913 birth cohort experienced a markedly excessive risk of MI with smoking during its first 4 years of observation (*275*); more than 90 percent of those who had myocardial infarctions were current smokers in comparison with 55 percent of those who did not. Subsequent analyses with 13-year followup have confirmed this strong relationship between smoking and CHD; the incidence of fatal

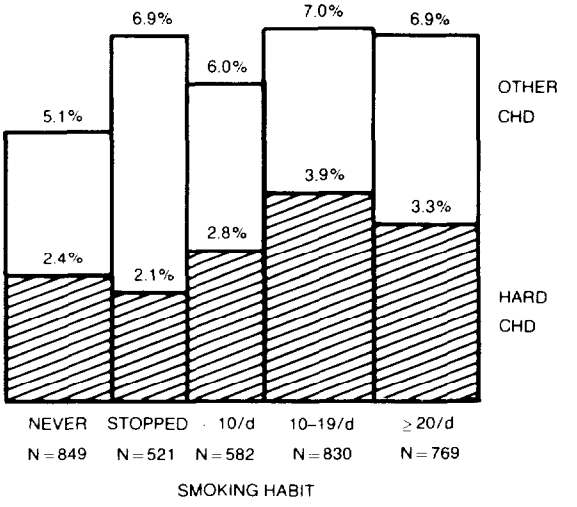


FIGURE 5.—Age-standardized 10-year incidence rate of coronary heart disease of 3,551 men in Italy and Greece (Crevalcore, Montegiorgio, Rome railroad, Crete, and Corfu), classified by smoking habit at entry and then free of cardiovascular disease

SOURCE: Keys (*143*).

and nonfatal MI increased with the quantity of daily tobacco consumption. Pipe and cigar smokers experienced an increased risk similar to cigarette smokers (*278*). No significant difference was observed for angina pectoris by smoking status.

Prospective data obtained in the Norwegian Vegetable Oil workers study beginning in 1965 have been analyzed with respect to risk factors measured at the baseline examination and the incidence of CHD during the following year (*199*). The defined sample comprised 16,608 men born between 1905 and 1916 who were employed in industries throughout Norway. Randomization to a control group or to a group receiving linolenic acid was performed in 13,000 men 50 to 59 years of age who were well and agreed to participate. Industrial physicians participated in the provision of baseline data and in the ascertainment of cases.

Fewer than the expected number of deaths occurred, but the number of deaths from CHD was intermediate between that expected on the basis of the Oslo and the total Norwegian populations. MI was observed in 162 men during the followup; there were no significant differences in CHD incidence attributable to treatment with linolenic acid.

TABLE 5.—First diagnosed myocardial infarction (probable + possible) in relation to cigarette consumption

Cigarettes per day	5 percent sample: No.	5 percent sample: Mean cholesterol	Men at risk[1]	Infarctions diagnosed in observ. yr	Rates percentage: Unadjusted	Rates percentage: Adjusted for age and: Weight/height ratio	Rates percentage: Adjusted for age and: Elevated sedimentation rate
None	228	239.8	5,693	37	.65	.63	.68
1–4	40	244.1	1,094	6	.55	.57	.57
5–14	162	245.2	3,679	56	1.52	1.59	1.46
15–24	47	240.7	1,214	13	1.07	1.11	1.00
25+	9	236.3	191	8	4.19	4.15	3.80
Unknown	126	237.0	4.304	42	.96		
	612	241.0	16,175	162	1.00		

[1] Men with no previous infarction diagnosis.
SOURCE: Natvig et al. (*199*).

The incidence of MI increased markedly with the level of cigarette smoking; the relative risk of MI for men smoking 25 cigarettes or more per day was over six times that of nonsmokers (Table 5). Smoking was less strongly related to angina pectoris (*199*).

The Oslo study examined and followed 14,000 men aged 40 to 49 who were free of cardiovascular disease and diabetes mellitus at examinations in 1972 and 1973. During 4 2/3 years of followup, searches of discharge records of Oslo hospitals and of death registration by the Oslo health department were used to identify nonfatal and fatal first MIs; sudden deaths without confirmation of MI were excluded (*117*). The incidence of MI in nonsmokers (never and ex-smokers) was only 40 percent of that in cigarette smokers (*117*).

A 10-year prospective study of men examined in 1964 at age 50 in Glostrup County, Denmark, was reported by Schroll and Hagerup (*240*). Out of a total population sample of 514 men, 436 were examined; followup for mortality and myocardial infarction was obtained in virtually all patients. This population resided in a middle-class suburb in the western part of Copenhagen and was thought to reflect the change in Danish society from principally agricultural to industrial and to be representative of the total Danish population in 1964. During the 10-year followup, 31 men developed first myocardial infarctions, an incidence of 7.1 percent. Fatal MI occurred in 16, and 15 experienced a nonfatal MI. A significantly higher risk of myocardial infarction was observed in those who smoked tobacco at baseline examination. The incidence was as follows: nonsmokers, 6 percent; smokers of 1–14 g per day, 6 percent; smokers of 15–24 g per day, 14 percent; smokers of 25 g or

TABLE 6.—Seven-year incidence of fatal and nonfatal first myocardial infarction in 3,772 smokers by category of smoking habit and 440 men who have never smoked

	Myocardical infarction per 1,000 men	Relative risk
Never smokers	17	1.0
Cigarette smokers		
Total	36	2.1
>10/day	43	2.5
Cigar smokers		
Total	42	2.4
>3/day	35	2.1
Cheroot smokers		
Total	48	2.8
>6/day	72	4.2
Pipe smokers		
Total	26	1.5
>6/day	34	2.0

SOURCE: Gyntelberg et al. (*91*).

more per day, 19 percent. Thus, the heavy smokers experienced an incidence of MI that was three times that of nonsmokers.

The incidence of fatal and nonfatal first myocardial infarctions in men was observed in 3,772 smokers and 1,440 nonsmokers who had baseline examinations in 1970 and 1971, were aged 40 to 59, and were employed in public and private Copenhagen companies (*91*). The initial response rate was 87 percent. Fatal MI was ascertained during 7 years of followup from death certificates; nonfatal MI was ascertained from 5-year followup by questionnaires (79 percent response rate) and from hospital records. Myocardial infarction among the nonresponders was included if recorded in the Copenhagen heart register, which registered all inpatient cases of myocardial infarction in the Copenhagen area.

During the followup period, 41 men free of coronary heart disease at baseline examination died from a first myocardial infarction and 129 men had a nonfatal first myocardial infarction. Overall, the relative risk of myocardial infarction was twice as high in smokers as in nonsmokers. The relative risk of fatal and nonfatal first MI in smokers compared with never smokers was as follows: cigarette smokers of more than 10 per day, 2.5; cigar smokers of more than 3 per day, 2.1; cheroot smokers of more than 6 per day, 4.2; and pipe smokers smoking more than six times per day, 2.0 (Table 6). In this study heavy cheroot smokers experienced the highest risk of MI.

Finnish men aged 50 to 53 years, insured for 10 or more years with a large Finnish life insurance company, were examined in 1965 and

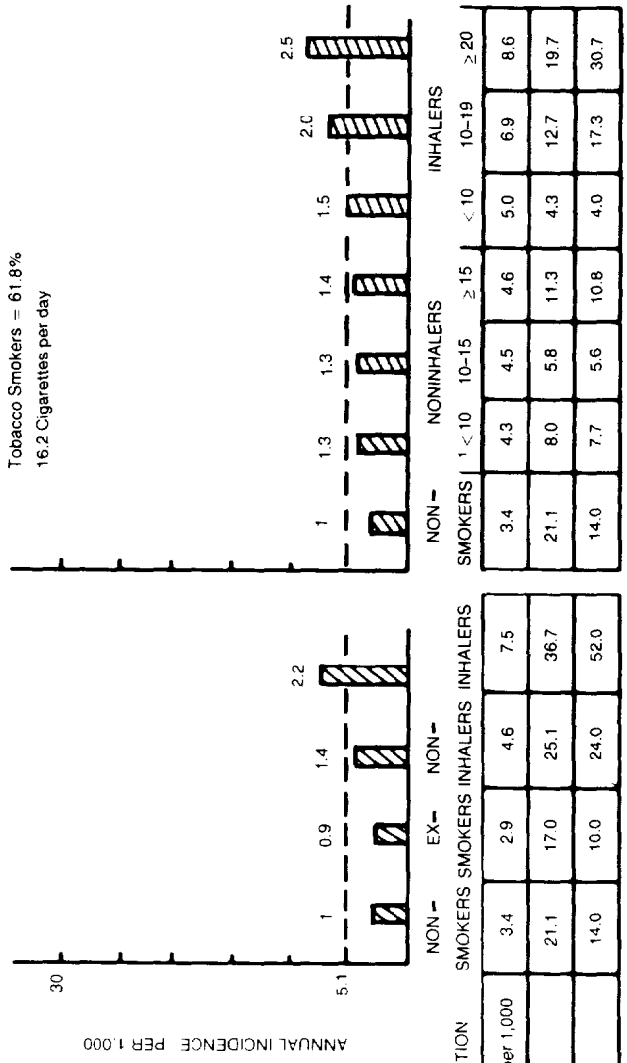
1966; the examined cohort (1,648 men) consisted of 40 percent of those respondents who had complete data (*207*). Risk factor data included serum lipids after a 12-hour overnight fast. A smoker was a person who smoked cigarettes regularly every day; pipe and cigar smokers as well as ex-smokers were excluded from the analysis of smoking effects. With these criteria, 567 men were smokers and 982 were nonsmokers. During 7 years of followup, all deaths were identified, and cause of death was determined from death certificate files. Cardiovascular deaths included those due to coronary heart disease, heart failure, cardiac arrhythmia, cerebrovascular accidents, and sudden deaths. Cigarette smoking was associated with increased cardiovascular mortality independently of other risk factors.

The North Karelia, Finland, project was started in 1972 to mobilize community intervention for health promotion and disease prevention (*235*). Substantial risk factor data were obtained from random population samples of two rural counties in eastern Finland. Analysis showed a strong relationship between the major risk factors at the baseline examination (smoking, hypertension, and serum cholesterol) and the subsequent development of CHD. The relationship of smoking to the incidence of acute myocardial infarction was independent of the other risk factors (*235*). Eastern Finland had the highest incidence and mortality from CHD in the world, but the rates have declined substantially coincident with decreasing prevalence of these risk factors (*235*).

A large defined cohort of men aged 42 to 53 years, born in France and employed in the Paris civil service, was observed for an average of 4 years (range, 2–7 years) following a baseline examination for risk factors in 1965 (*218*). Those with definite Q waves on initial examination were excluded, leaving 7,453 men at risk. Criteria for CHD were based on those of the Pooling Project and the London Whitehall study (*51, 218*).

The overall incidence of CHD was 5.1 per 1,000; MI and CHD deaths accounted for 60 percent of the cases, while 40 percent of the cases were due to angina pectoris. Cigarette consumption, hypertension, hypercholesterolemia, and clinical diabetes mellitus were independently related to the incidence of coronary heart disease. Men in their fifties had a strikingly lower incidence of CHD than men in the United States; this is consistent with French mortality statistics. In univariate analysis, the incidence of CHD was progressively higher with increasing number of cigarettes smoked per day among inhalers; noninhalers had an intermediate risk (Figure 6) (*218*).

A defined cohort of 10,232 Israeli civil servants and municipal workers (86 percent of the defined sample) aged 40 years and above were first examined in 1963 and followed for fatal and nonfatal MI



TOBACCO CONSUMPTION	NON-SMOKERS	EX-SMOKERS	NON-INHALERS	INHALERS
Incidence per 1,000	3.4	2.9	4.6	7.5
Population	21.1	17.0	25.1	36.7
Patients	14.0	10.0	24.0	52.0

NON-SMOKERS	NONINHALERS				INHALERS			
	[1] < 10	10–15	≥ 15	< 10	10–19	≥ 20
3.4	4.3	4.5	4.6	5.0	6.9	8.6
21.1	8.0	5.8	11.3	4.3	12.7	19.7
14.0	7.7	5.6	10.8	4.0	17.3	30.7

FIGURE 6.—Risk of ischemic heart disease as a function of tobacco consumption (average observation, 4 years)

[1] Cigarettes per day.

SOURCE: Richard et al. (*218*).

and sudden cardiac death (*177*). Reexaminations were performed in 1965 (97.5 percent reexamination rate) and again in 1968 (98 percent reexamination rate). After 5 years of followup, 9,764 were found to be free of myocardial infarction and there were 427 incidence cases (44 per 1,000). Of these 170 (40 percent) were unrecognized myocardial infarctions, half of which had been asymptomatic. The incidence of CHD was significantly related to the daily use of cigarettes, and the relative risk was greater at younger age (*81, 176*). In multivariate analysis the relationship of smoking to CHD became stronger when other variables were taken into account (*81*).

In summary, there were marked differences in CHD rates for the populations in different countries and different geographic locations. The relationship between cigarette smoking and CHD was more pronounced in those countries with high CHD rates. However, even in those countries with low CHD rates the evidence increasingly suggests a relationship between cigarette smoking and CHD.

Cigarette Smoking and Other Risk Factors

The strong relationship between cigarette smoking and CHD has been shown to be independent of the other major risk factors in a number of well-designed epidemiologic studies. A number of other factors have also been described as having an influence on CHD risk (*119, 124, 133, 159, 214, 251*). The magnitude of excess risk observed with these minor risk factors has usually been small in comparison with the excess risk observed with the major risk factors (*40, 68, 143, 214*).

The independence of the relationship between cigarette smoking and CHD risk has been observed in a straightforward fashion. The excess risk of CHD in smokers compared with nonsmokers exists at both high and low levels of the other risk characteristics associated with CHD. Also, extensive experience has shown that confounding influences can be separated out with multiple logistic analysis (*147*). Such analyses with adjustment for potentially confounding influences have been made for many characteristics in many of the studies cited in this Report. They include hypertension, elevated serum cholesterol, obesity, family history of CHD, diabetes mellitus, physical inactivity, certain personality characteristics, psychological stress, socioeconomic status, and intake of alcohol and coffee. When the data have been sufficient for adequate analysis, excess risk of CHD has been observed in cigarette smokers independent of the presence (or absence) of other CHD-risk-conferring characteristics. Such observations, made in a very large number of studies, indicate that it is the cigarette smoking habit itself that confers high risk of CHD rather than an associated characteristic (*18, 40, 43, 45, 67, 94, 96, 143, 214, 244, 257*).

Behavioral characteristics other than cigarette smoking have been considered important in relation to CHD, but relatively few studies of behavioral characteristics have been conducted in the context of standardized examinations of defined cohorts with consideration of potentially confounding variables. The Western Collaborative Group Study (WCGS) in California met these conditions, and therefore this study will be considered in some detail (*24, 66, 71*).

In the WCGS (*229*), 3,154 employed men examined in 1960–1961 and found to be free of CHD were characterized for behavioral pattern by a structured interview developed for this purpose and administered by trained interviewers. From tape recordings of interviews, reviewers who had no knowledge of the subjects' history or other characteristics classified the men as Type A personalities according to their manifestation of enhanced aggressiveness, ambitiousness, competitive drive, and chronic sense of time urgency. The men were classified as Type B personalities if they manifested less of the Type A characteristics and were more calm and relaxed. The Type A pattern was determined in 1,067 and the Type B pattern in 1,182 of the subjects at risk. Previously recognized risk factors were also measured. Mortality surveillance was obtained, and final followup examinations were performed for this population in 1969.

With an average followup of 8.5 years, there were 140 deaths; 31 were attributed to an initial CHD event, 19 to a recurrent CHD event, and 90 to non-CHD causes, including 7 who had developed CHD prior to the onset of the non-CHD terminal illness. CHD incidence was observed in 257 cases. Autopsy examination was performed in 24 of 31 decedent cases; acute coronary thrombosis or acute myocardial infarction was observed in 23, and severe diffuse coronary atherosclerosis was observed in 1 case.

CHD death was ascertained in 34 Type A and 16 Type B subjects. The CHD death rate per 1,000 person-years was 2.92 for Type A and 1.32 for Type B subjects.

As would be expected from other studies, the CHD incidence cases were older, smoked more cigarettes, were heavier, and had higher systolic and diastolic blood pressures, higher serum cholesterol and triglyceride levels, and higher ratios of beta to alpha lipoproteins. Other positive associations were a history of diabetes mellitus, parental history of CHD, low level of education, and low level of leisure time activity. Occupational physical activity and annual income were not significantly related to CHD incidence.

Cigarette smoking was significantly related to the incidence of CHD, and the risk was higher with increasing numbers of cigarettes smoked at the time of the baseline examination; the relative risk with smoking in older men was as great as in the younger men.

By personality patterns, those who had been characterized as Type A had an incidence of CHD that was twice as high as the incidence in

those who had been characterized as Type B. This difference persisted after adjustment for the other risk factors. In both deciles of age at entry (39–49 and 50–59), the relative risks for current cigarette smokers were higher than for nonsmokers in both Type A and Type B personalities (Table 7) (*229*).

A multiple logistic equation describing the relationships of the conventional risk factors to the incidence of CHD in this study was similar to the Framingham study equation (*25*). The coefficients for the two studies were not significantly different. Cigarette smoking, serum cholesterol, and systolic blood pressure were independent risk factors and were significantly related to the CHD incidence. The total number of cases and the number by decile of risk were similar, using the equation developed from the WCGS data and the equation from the Framingham study, indicating good relative agreement in risk prediction. In the WCGS analysis, the Type A behavior pattern was found to predict the incidence of CHD independently of the other risk factors. The additional predictive power of the Type A characteristic in the multiple logistic equation was related to some extent to higher levels of the conventional risk factors in Type A individuals.

Evidence for the importance of personality characteristics was also observed in the Framingham cohort and in studies by the French–Belgian Collaborative Group (*66, 104*). In these studies as well, the effect of cigarette smoking on CHD remained independent of personality characteristics.

In summary, the evidence from studies with adequate data have clearly demonstrated that cigarette smokers experience higher risk of CHD regardless of their other behavioral characteristics.

Interaction of Cigarette Smoking and Other Risk Factors

A number of pharmacologically active substances are present in tobacco smoke, and a number of direct physiologic effects have been observed (*262*) and are reviewed elsewhere in this Report. Recently, evidence has accumulated of an effect of smoking on lipoproteins. Recent population studies have demonstrated an inverse relationship between high density lipoprotein cholesterol (HDL-C) and the incidence of CHD (*80, 84, 217*). Population groups known to be at lower risk for CHD have been observed to have relatively high levels of HDL-C. Thus, HDL-C levels have been higher in women in comparison with men, in black men in comparison with white men, and in men in Japan in comparison with men in the United States (*5, 106, 146, 260*). An adverse influence of cigarette smoking on the levels of HDL-C and other plasma or serum lipoprotein components has been observed in a number of populations. The several classes, or fractions, of these lipid–protein complexes have different functions

TABLE 7.—Prospective history and findings by behavior pattern

	Age 39–49 years						Age 50–59 years					
	Subjects at risk		Subjects with CHD[1]		Rate of CHD[2]		Subjects at risk		Subjects with CHD		Rate of CHD[2]	
	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B
Number of subjects	1,067	1,182	95	50	10.5	5.0	522	383	83	29	18.7	8.9
Parental history of CHD												
Yes	214	197	23	15	12.6	9.0	103	64	20	7	22.8	12.9
No	853	935	72	35	9.9	4.2	419	319	63	22	17.7	8.1
Smoking habits												
Never smoked	221	315	11	8	5.9	3.0	90	89	10	5	13.1	6.6
Pipe or cigar	191	216	11	6	6.8	3.3	81	78	17	2	24.7	3.0
Former cigarette	110	129	11	5	11.8	4.6	91	41	10	2	12.9	5.7
Current cigarette	545	522	62	31	13.4	7.0	260	175	46	20	20.8	13.4
Current cigarette usage												
None	522	660	33	19	7.4	3.4	262	208	37	9	16.6	5.1
1–15/day	95	119	3	8	3.7	7.9	65	43	8	1	14.5	2.7
≥16/day	450	403	59	23	15.4	11.4	195	132	38	19	22.9	16.9
Systolic blood pressure, mm Hg												
<120	264	328	17	4	7.6	1.4	95	80	7	4	8.7	5.9
120–159	771	826	69	43	10.5	6.1	381	283	64	21	19.8	8.7
≥160	32	28	9	3	33.1	12.6	46	20	12	4	30.7	23.5
Diastolic blood pressure, mm Hg												
<95	970	1,100	81	45	9.8	4.8	448	344	64	25	16.8	8.5
≥95	97	82	14	5	17.0	7.2	74	39	19	4	30.2	12.1

TABLE 7.—Continued.

	Age 39–49 years						Age 50–59 years					
Serum cholesterol, mg/100 ml												
<220	486	607	24	11	5.8	2.1	211	148	20	6	11.2	4.8
220–259	352	376	32	20	10.7	6.3	179	142	36	10	23.7	8.3
≥260	226	195	39	19	20.3	11.5	130	90	27	13	24.4	17.0
Fasting serum triglycerides, mg/100 ml												
<100	252	348	12	7	5.6	2.4	151	99	16	5	12.5	5.9
100–176	500	538	48	22	11.3	4.8	238	170	37	11	18.3	7.6
≥177	247	249	30	20	14.3	9.6	114	98	26	9	26.8	10.8
Serum β-/α-lipoprotein ratio												
<2.36	733	836	57	24	9.1	3.4	323	263	43	18	15.7	8.1
≥2.36	331	343	38	26	13.5	8.9	196	117	39	11	23.4	11.1

[1] Coronary heart disease.

[2] Average annual rate/1,000 subjects at risk. Difference in rates between type A and type B was tested for significance by Mantel-Haenszel χ^2, with adjustment for factors indicated. For each factor, the adjusted association between behavior pattern and CHD incidence is signficant at $p < .001$.

SOURCE: Rosenman et al. (*229*).

in lipid metabolism (*41, 78, 213*). Most of the cholesterol in the plasma is complexed in the low density lipoprotein cholesterol (LDL-C) fraction, which appears to have atherogenic properties, while a lesser proportion of cholesterol is complexed with high density lipoprotein cholesterol (HDL-C), which appears to have antiatherogenic properties (*82, 100, 180, 230*).

The HDL-C levels in the cigarette smokers in the studies cited above have been found to be significantly lower than in nonsmokers, and in some studies the concentration of HDL-C has been found to correlate inversely with daily cigarette consumption. This relationship does not appear to be confounded by other factors. Thus, HDL-C is inversely correlated with indices of obesity, such as relative weight, and positively correlated with alcohol intake; adjustment for these characteristics increases the difference in HDL-C between cigarette smokers and nonsmokers (*79, 99, 105, 212*). Additional studies are needed to investigate the complex mechanisms whereby cigarette smoking depresses HDL-C levels and increases the risk for CHD.

Blood pressure increases transiently after smoking, mediated by an adrenergic mechanism (*37*); however, most surveys have demonstrated a small negative association between smoking and blood pressure (*263*). Recent investigations of this relationship have adjusted for the covariables of weight and alcohol.

In an examination of the offspring of Framingham heart study patients and their spouses, multivariate analysis demonstrated a negative correlation between smoking and blood pressure, especially diastolic blood pressure, that was similar to the original Framingham cohort (*102*). A cross-sectional survey of employed men in Australia also demonstrated that, adjusted for weight and alcohol, diastolic blood pressures were slightly lower in smokers (*5*). In the cohort of the Lipid Research Clinics prevalence study, the small negative correlation between smoking and blood pressure was more apparent for systolic blood pressure (*36*). In the cross-sectional and prospective analyses of several study populations in Chicago, however, smoking was associated with higher blood pressure, especially systolic blood pressure (*52, 53*). Alcohol consumption was not included in these multivariate analyses.

If smoking is associated with a slightly lower blood pressure, a rise in blood pressure might be predicted after smoking cessation, especially if smoking cessation is followed by weight gain, but recent studies have not supported this concern. In the Kaiser population, smoking cessation has been associated with only a small weight gain (*70*). Effects on blood pressure were also small and inconsistent among subgroups. In the Multiple Risk Factor Intervention Trial, smokers who quit lost less weight than those who did not quit (*239*); controlling for weight, there was no increase in blood pressure with

smoking cessation. These studies show that there is little, if any, adverse effect on risk factors following smoking cessation. The benefits of smoking cessation for health in general, and cardiovascular health in particular, far outweigh any objectively observed disadvantageous effect.

Although epidemiologic studies do not suggest that smoking causes high blood pressure, concern has been expressed that it may exacerbate the clinical course. Two case–control studies in Great Britain (*20, 125*) and one in New Zealand (*57*) compared smoking patterns in patients with malignant or accelerated hypertension with those with benign hypertension. In all three, statistically significant associations between smoking and the more severe manifestations of hypertension were demonstrated.

A recent clinical study directly observed the blood pressure effects of smoking in mild hypertensives (*65*). When 16 habitual smokers abstained from cigarettes, their blood pressure was significantly lower than usual. Smoking two cigarettes resulted in a blood pressure increase of 10/8 mm Hg that lasted approximately 15 minutes. Combining coffee drinking with smoking led to an increase in blood pressure to their usual levels that lasted 2 hours.

For the most part, recent surveys have supported the traditional finding of a small negative association between smoking and blood pressure. Smoking cessation is not associated with a significant increase in blood pressure, especially if weight gain is avoided. Preliminary studies suggest that smoking increases the likelihood of developing malignant hypertension. Prospective and intervention studies are indicated to further investigate this phenomenon.

These findings can be translated into clinical recommendations: (1) nonhypertensive smokers can be assured that smoking cessation will not lead to high blood pressure, especially if weight gain is avoided, and (2) hypertensive smokers should be warned that these two risk factors are synergistic for cardiovascular disease and that the need for risk reduction is increased. Smoking cessation will not complicate the management of high blood pressure, and may reduce hypertensive complications. Concomitant monitoring of weight during and after smoking cessation is indicated.

Synergistic Effects of Cigarette Smoking When Associated With Other Risk Factors

Evidence that the increase in CHD risk associated with smoking may be greater when other risk factors are present than when they are absent has been observed in several investigations. Figure 7 presents the data from the Framingham 12-year followup. The CHD risk increases with increasing levels of blood pressure or serum cholesterol, and at each level of these two risk factors the risk in

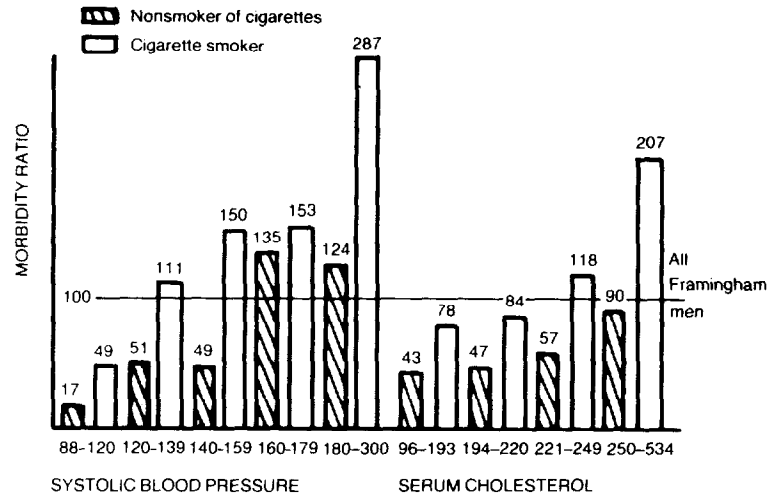


FIGURE 7.—Cigarette smoking at levels of blood pressure and serum cholesterol, 12-year incidence

NOTE: The contribution of cigarette smoking to risk of coronary heart disease appears to be independent of other demonstrated risk factors. At any level of blood pressure or serum cholesterol, cigarette smokers had an excess risk, 12-year incidence.

SOURCE: Kannel (*132*).

smokers is greater than the risk in nonsmokers. However, the increment of risk with smoking is not constant, but rather increases with increasing levels of blood pressure or cholesterol. For example, in Figure 7 the increment in risk in smokers with a systolic blood pressure of 80–120 mm Hg is 32 (49 minus 17), while the increment for smokers with a systolic blood pressure of 140–159 is 101 (150 minus 49). These data suggest that cigarette smoking interacts with the other two major risk factors to produce a combined risk that is greater than the sum of the risks that would have been produced by the same risk factors acting separately.

Pooling Project data are also consistent with a synergistic effect of cigarette smoking with hypertension and hypercholesterolemia (Figure 8) (*19*). Evidence of synergism has been found in other studies as well. In the Ni-Hon-San study, the effect of cigarette smoking on CHD incidence in the presence of high serum cholesterol appeared to be more than additive in Japanese Americans living in Hawaii. The same effect was not observed in Japanese men living in Japan, who in general had substantially lower serum cholesterol levels (*221*). Evidence of synergism was observed in the Stockholm prospective study and the Göteborg studies (Figure 9) (*27, 278*).

The synergistic interaction between the major risk factors may also explain the observation that the actual incidence of CHD in

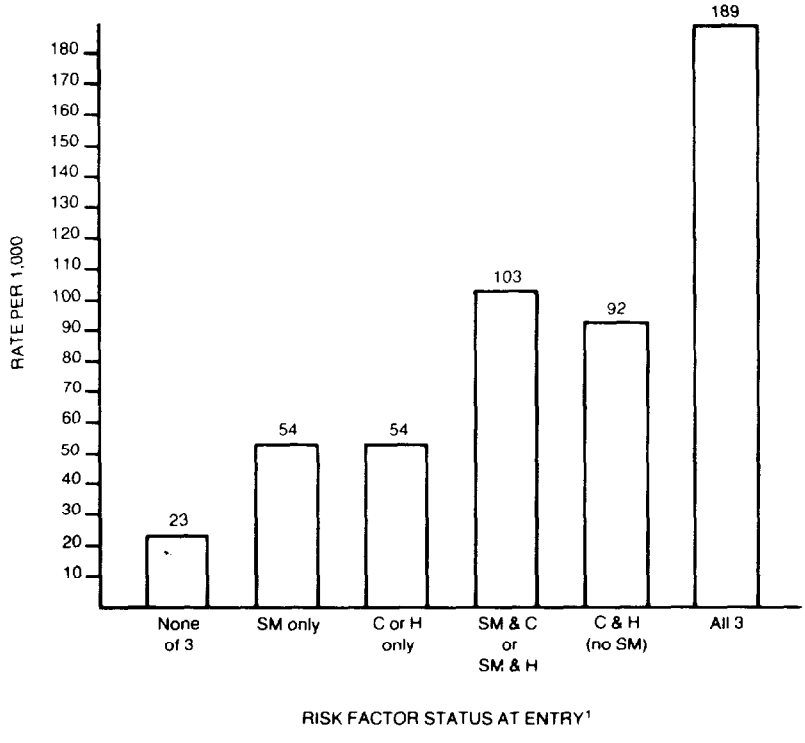


FIGURE 8.—Major risk factor combinations, 10-year incidence of first major coronary events, men age 30–59 at entry, Pooling project

[1] Definitions of the three major risk factors and their symbols: hypercholesterolemia (C), ≥ 250 mg/dh; elevated blood pressure (H), diastolic pressure ≥ 90 mm Hg; cigarette smoking (SM), any current use of cigarettes at entry.

NOTE: All rates were age adjusted by 10-year age groups to the U.S. white male population, 1980.

SOURCE: The Pooling Project Research Group (*214*).

populations with low levels of serum cholesterol is substantially lower than the incidence predicted by the multiple logistic equations derived from the Framingham population (*85, 91, 124, 143, 146*). If the synergistic interaction is present at low levels of the major risk factors to the same degree as at high levels of risk factors, then the impact of cigarette smoking on blood pressure in a low cholesterol population would be expected to be smaller than that measured in high cholesterol populations such as in the United States and Western Europe. The multiple logistic equations do not separate out effects that are due to synergistic interactions, and they distribute the synergistic effects to the separate risk factors as though there were no interaction among the risk factors in producing CHD. These equations treat the risk factors as though the effects of the risk

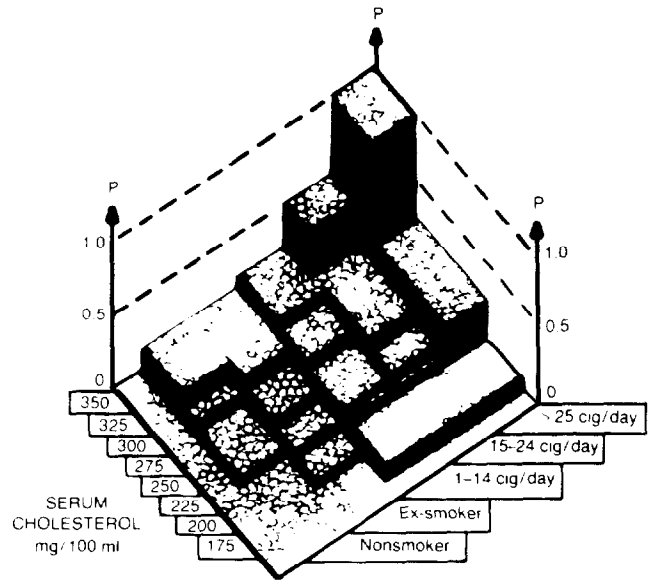


FIGURE 9.—Risk factors for disease according to population studies

NOTE: P = probability of nonfatal and fatal myocardial infarction for a 50-year-old man during 13 years' followup, 855 men born in 1913.

SOURCE: Wilhelmsen (*278*).

factors were additive. This limitation of the multiple logistic equation technique leads to an overprediction of the number of CHD cases to be expected in a population on the basis of smoking habits when that population has very low levels of another major risk factor such as serum cholesterol levels. Therefore, the very low levels of CHD observed in cigarette smokers from populations with very low serum cholesterol levels may reflect the synergistic nature of the interaction among the major risk factors rather than the absence of a CHD risk associated with cigarette smoking in those populations. The possibility also exists that the cigarette smokers in some of these populations have not been smoking for a sufficient duration or with a sufficient intensity to manifest an effect on coronary artery disease.

Analytical and methodological refinements appear to be needed for better understanding of the biological significance of synergism (*147*). Nevertheless, the evidence is clear that cigarette smoking greatly increases the risk of CHD in individuals already at increased risk because of other risk factors.

Risk of CHD in Women

Young and middle-aged women experience only one-fifth the incidence and mortality from CHD of men (*16, 40, 94, 101, 139, 244, 255, 283*). These rates are steeply age dependent, and rates in young and middle-aged women lag behind those in men by about 10 years. Reasons for the sex-dependent differences are incompletely understood, but this protective influence of female sex is partly due to differences in cigarette smoking and other behavioral variables (*6, 58, 103, 127, 128, 150, 151, 166, 170, 203, 204, 210, 227, 234, 243, 244, 255, 267, 270, 280*).

During the 1950s and 1960s, when the previously reported large-scale investigations of smoking and CHD were conducted, relatively few women smoked, and on the average, those who did began at an older age, smoked fewer cigarettes, and inhaled less than men (*261*). During the past two decades, women have begun to smoke cigarettes at younger ages, and their cigarette smoking habits have become more like those of men (*261*). Observations by a number of investigators have shown that the incidence of CHD in recent years in women who smoke cigarettes is far greater than the very low rates that are observed in women who do not smoke, and the incidence of CHD in women who smoke heavily may be similar to the incidence in men.

To observe the effect of cigarette smoking in women more specifically, studies have been performed to take account of potentially confounding influences on the occurrence of CHD. Slone et al. (*244*) in Boston observed cases and matched controls from a large number of U.S. hospitals between July 1976 and December 1977. During this 18-month period, 55 cases of nonfatal MI were identified in women under age 50 who had not used oral contraceptives within the month prior to admission and who had not been under treatment for heart disease or related disorders. The estimated relative risk for smokers compared with nonsmokers was 6.8 ($p < 0.001$). In light smokers (1 to 14 cigarettes per day) the relative risk was 4.4, and in heavy smokers (more than 35 cigarettes per day) the relative risk was 21. The relative risk appeared as great in those who had not experienced menopause as in those who had experienced menopause. In those young women with no known risk factors other than cigarette smoking, the data indicated that the smoking habit accounted for 76 percent of the risk of nonfatal MI (*244*). This magnitude of relative and attributable risk with smoking in otherwise healthy young women is consistent with similar observations in young men.

A subsequent report included cases observed through August 1978 with and without the following characteristics: obesity, diabetes mellitus, abnormal blood lipids, hypertension, angina pectoris, history of preeclampsia, coffee consumption, and oral contraceptive

(OC) use (*227*). Smoking was confirmed as a singularly strong risk factor (Figure 10). Relative risk increased exponentially with the number of cigarettes smoked, and the relative risk in younger women was greater than in older women. A gradient of risk with increasing level of cigarette smoking was also observed in subjects who had one or more of the other risk factors. In those at the highest level of risk, women smoking 35 or more cigarettes per day who had one or more predisposing risk factors, the relative risk was 31.

A number of investigations have been performed to observe the effects of OC use, and there is substantial evidence for interaction of the smoking effect with OC use as well as other risk factors. These data suggest that the biological effect of multiple risk factors, particularly when combined with OC use, may be multiplicative for the risk of CHD. Shapiro et al. (*242*) found that women who smoked more than 25 cigarettes per day but did not use OCs experienced a relative risk of MI of 7 in comparison with nonsmoking women who did not use OCs. Nonsmokers who used OCs experienced a relative risk of MI of 4.5. The women who combined both behaviors had a relative risk of MI of 39. In a case–control study of factors related to MI in nurses in the United States, Rosenberg et al. (*226*) reported relative risks with OC use, smoking, and hypertension of 3, 5, and 8, respectively; however, in nurses with all three characteristics the relative risk was 170.

Comparable results were observed in England by Mann, where the relative risk for MI in women with major cardiovascular risk factors (including cigarette smoking) who used OCs was up to 128 times that of women free of these characteristics (*169*). The importance of cigarette smoking to the incidence of MI in women has been confirmed by other studies in England (*211, 270*), Sweden (*16, 279*), Scotland (*203*), Finland (*234*), and elsewhere.

In addition to the excess risk of nonfatal MI and death from CHD, sudden cardiac death in women has been observed to be strongly related to the cigarette smoking habit (*249, 254*). However, the relationship of angina pectoris to cigarette smoking is uncertain. As in men, some studies have shown a positive relationship with smoking (*271*), but other studies have found no significant difference in the occurrence of angina pectoris between female smokers and nonsmokers (*16, 40, 203*).

CHD incidence and mortality in women increase remarkably after the menopause. Before the menopause, cases of CHD may be limited largely to women who smoke (*15, 16, 138*). Furthermore, there is evidence that the menopause occurs at an earlier age in women who smoke than in women who do not smoke (*129, 270*). Willet et al. (*282*) observed a progressive increase in the risk of early menopause with an increasing level of daily use of cigarettes, and cigarette smoking was more closely related to early menopause than any other factor

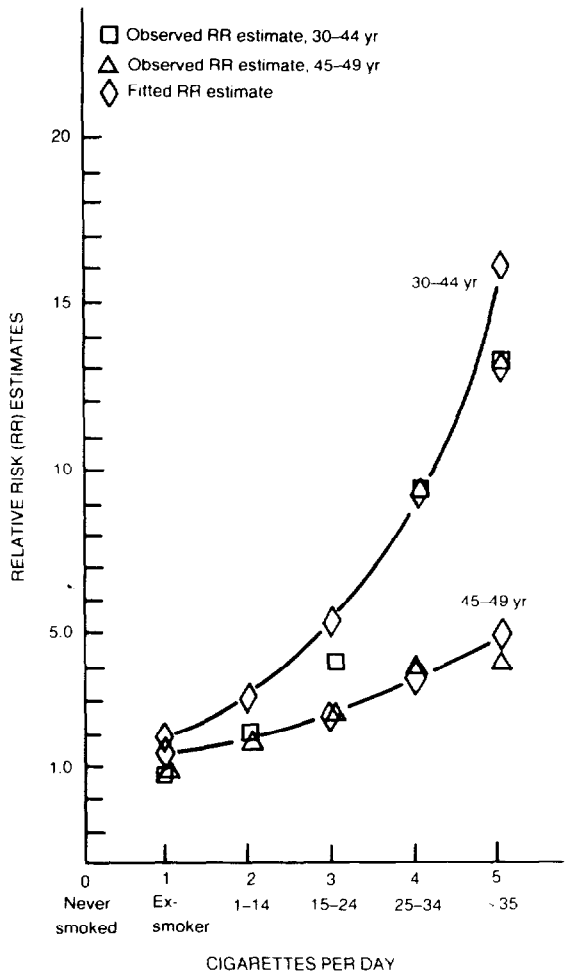


FIGURE 10.—Relation to relative risk of myocardial infarction to cigarette smoking, according to age

NOTE: Difference in slopes: $\chi_1^2 = 2.7$, $p_2 = 0.10$.
SOURCE: Rosenberg et al. (*227*).

considered. The evidence that a combination of cigarette smoking with the use of oral contraceptives potentiates (multiplies) the occurrence of CHD is strong, but the mechanisms are not adequately understood. The use of noncontraceptive estrogens was not associated with an excess risk of MI (*228*). Furthermore, menopausal estrogen therapy has been associated with a protective effect from CHD death (*231*). There is evidence that both cigarette smoking and

progestins in oral contraceptives depress high density lipoprotein cholesterol (HDL-C), and HDL-C appears to protect from CHD (*13, 23, 35, 41, 59, 62, 74, 78, 122, 123, 213, 215, 265, 266, 269, 281*). Those with low levels of HDL-C have been shown to suffer higher rates of CHD than those with high levels of HDL-C (see Interaction of Cigarette Smoking and Other Risk Factors above).

Whatever the mechanism, it must be concluded that women who decide to smoke assume a substantially increased risk of CHD, and that the risk for women who smoke heavily approaches the risk of CHD for men. The relative risk of cigarette smoking is greater in younger women than in older women, and the relative risk increases progressively with the number of cigarettes smoked. Women who smoke have been observed to experience menopause earlier than women who do not smoke, and this may also increase the CHD risk for women who smoke. A synergistic interaction between cigarette smoking and other risk factors for CHD has been demonstrated for women, particularly for oral contraceptive use. More investigation is required to evaluate this phenomenon; an astonishingly high relative risk of CHD occurs in women who smoke cigarettes and also have other risk factors, including use of oral contraceptives.

Risk of Sudden Cardiac Death

The definition of sudden cardiac death (SCD) is discussed in the introduction to this section. In a number of studies, severe CHD has been observed in a large proportion of the cases that have succumbed to SCD (*10, 12, 139, 153, 154, 156, 157, 160, 162, 200, 208, 248*).

In several epidemiologic studies, cigarette smoking has been even more closely related to SCD than to CHD in general. After 24 years of followup in the Framingham study (*40, 139*), the risk of SCD in cigarette smokers was found to be three times that in nonsmokers, and a comparable relative risk was observed in the five-cohort Pooling Project data (*124, 251*). Although the relative risk in young men was greater than in older men, the relative risk was 2 even in men aged 70 to 79 in the Framingham cohort (*40*). In the Pooling Project data, the 10-year incidence of SCD increased progressively with the number of cigarettes smoked per day, analogous to the relationships with the first major coronary event or with all CHD deaths (*124, 251*). Other studies confirming the importance of cigarette smoking in SCD include members of the Kaiser-Permanente health plan in the San Francisco Bay area (*68*), black and white men and women in Baltimore (*156*), men employed in the telephone industry throughout the United States (*110*), and men living in Scandinavia (*72, 220*).

Other risk factors used to predict the occurrence of SCD include hypertension, high relative weight, high serum cholesterol, left ventricular hypertrophy by electrocardiogram, and alcoholism (*50,*

64, 68, 109, 137, 139, 149, 152, 153, 156, 173, 188, 209, 216). In multivariate analysis of the combined Framingham and Albany data for men aged 45 to 64, cigarette smoking emerged with the highest level of statistical significance among five risk factors predicting SCD (*137*).

Approximately half of those who experience SCD have preexisting clinical evidence of CHD (*109, 139, 153, 154, 220*). In a study by the Health Insurance Plan of Greater New York it was found that in comparison with patients who stopped smoking, those who continued to smoke after myocardial infarction or after the onset of angina pectoris experienced twice the risk of death over the subsequent 4 1/2-year period of followup (*242*). Results supporting this observation have been observed in some other studies (*69, 141, 155, 233, 238, 250*).

The results of numerous studies have consistently identified cigarette smoking as a leading factor in SCD. This is true for men and women, and the risk increases with the number of cigarettes smoked per day.

Prospective Mortality Studies

The detailed epidemiologic studies of CHD incidence described elsewhere in this section establish the close association between cigarette smoking and the subsequent development of coronary heart disease. The possibility that this association can be confounded by other characteristics with which smoking is associated has been intensively examined in these studies. The relationship between cigarette smoking and CHD has been demonstrated to exist independent of the presence of other risk factors.

Studies using CHD mortality as an end point can be performed at a lower cost than can studies of the incidence of the disease. This allows the inclusion of larger numbers of individuals in order to examine the effects of smoking in larger segments of the population. It also provides sufficient numbers of cases for detailed analyses of the effects of dose, age, smoking cessation, and other variables of interest. Studies examining the relationship between cigarette smoking and subsequent CHD mortality are now available for a variety of populations and include over 20 million person-years of observation. In the 10 largest studies the results are remarkably similar. Whether in the United States, Canada, the United Kingdom, Scandinavia, or Japan, smokers as a group experience excess CHD mortality that is approximately 70 percent above that of the nonsmokers.

In the following paragraphs, the major studies that have prospectively examined the relationship between cigarette smoking and CHD mortality are discussed. The number of individuals followed in these studies allows a detailed examination of the nature of this

relationship, including the changes in risk that occur with age, the relationship between dose of cigarette exposure and CHD risk, the effects of low tar and nicotine cigarettes, the risk of pipe and cigarette smoking, and the benefits of cessation.

Overall CHD Risk for Men and Women

A number of major prospective studies have examined the relationship between cigarette smoking and CHD mortality in men and women. Under this heading, a description of the populations studied and the findings for overall CHD risk in those populations are presented. Under subsequent headings, the questions of the differences in risk that occur with age, increasing dosage of cigarette exposure, low tar and nicotine cigarettes, pipe and cigar smoking, and the effects of cessation are examined on the basis of the evidence from these prospective studies.

In the United States, Dorn initiated a study of U.S. veterans who had served in the Armed Forces between 1917 and 1940 and who had U.S. Government life insurance policies in force in December 1953. This initial cohort of 293,658 persons was mailed a questionnaire in 1954, and the nonrespondents were followed up again in 1957. Responses were obtained from 248,046 veterans, with an overall response rate of 85 percent. Reports for 2 1/2 years (*46*) and 8 1/2 years (*131*) of followup were reviewed in detail in prior reports of the Surgeon General. The 16-year followup has been completed by Rogot and Murray (*224*). Death certificates were located for 85,323 (98 percent) of those original questionnaire respondents who died. Confirmation of the cause of death shown on the death certificate was investigated by Dorn (*46*). Whenever a death occurred in the United States, clinical confirmation concerning cause of death was sought from the physician who signed the death certificate. A response was obtained in 99 percent, and after review of the cause of death based on clinical data, only 6 percent of the deaths were reassigned to a cause different from that originally indicated on the death certificate. This degree of confirmation is considered good. Coronary heart disease mortality was 58 percent higher in cigarette smokers than in nonsmokers (Table 8), and CHD accounted for more excess deaths than any other cause of death.

In 1952, the 9-State study by the American Cancer Society was initiated; 187,783 white males, aged 50 to 70, were followed for an average of 44 months. There were 11,870 deaths. Of these deaths, 5,297 were due to coronary heart disease (*96*). A highly significant excess mortality was observed in smokers as compared with nonsmokers. The death rate for coronary heart disease was 70 percent higher in smokers compared with nonsmokers (Table 8).

In late 1959 and early 1960, the American Cancer Society enrolled 1,078,894 men and women from 25 States in a prospective study that

TABLE 8.—Coronary heart disease mortality ratios, major prospective studies

Population/ Study	Size	No. of CHD deaths	Mortality ratio		Comments
			Nonsmoker	Cigarette smoker	
U.S. veterans	290,000 males	34,874	1.00	1.58	
ACS 9-State study	188,000 males	5,297	1.00	1.70	
Japanese in 29 health districts	122,000 males 143,000 females	3,351 2,653	1.00 1.00	1.71 1.78	
ACS 25-State study	358,000 males 483,000 females	10,771 4,048	1.00 1.00	1.90–2.55 *	Male data for two levels of smoking intensity, see Table 12; *female data available by age and amount smoked only, see Tables 9 and 14
Canadian veterans	78,000 males	3,405	1.00	1.60	
British physicians	34,000 males 6,195 females	3,191 179	1.00 1.00	1.62 *	*Female data available by amount smoked only, see Tables 9 and 12
Swedish study	27,000 males 28,000 females	916 457	1.00 1.00	1.70 1.30	
California males in 9 occupations	68,000 males	1,718	1.00	1.60	
Swiss physicians	3,749 males	280	1.00	1.33–2.18	Data available by amount smoked only, see Table 12

was the largest of its kind ever conducted. All segments of the population were included, with the exception of groups that could not be easily traced. An initial demographic questionnaire recorded height, weight, detailed information concerning smoking (types of tobacco used, number of cigarettes smoked per day, inhalation, age at which smoking began, brand of cigarettes used), and other variables that might influence mortality. Hammond reported cause-specific mortality for the initial followup through September 1963 (97.4 percent successfully traced) on all those aged 35 to 84 at the time of enrollment (*93*). In men, 1,639,211 person-years of experience were observed, and in women, 2,125,360 person-years of experience were observed. Death certificates were obtained in 97.9 percent of the 25,895 deaths. CHD mortality ratios in male cigarette smokers

compared with those who never smoked regularly varied from 2.81 in men aged 45 to 54 to 1.24 in men aged 75 to 84 (Table 9). Ratios for women were 2.00 and 1.19 for age 45 to 54 and 75 to 84, respectively. In the 6-year followup reported by Hammond and Garfinkel (*94*), there was a total of 28,446 deaths. Using the death rates of nonsmokers as the standard, over 11,500 excess deaths were attributable to smoking. Coronary heart disease accounted for 46 percent of the excess deaths in men and 40.6 percent of the excess deaths in women.

A study of California men in various occupations was begun in 1954, and 68,153 men aged 35 to 64 were followed for mortality through December 1962 (*234*). Smokers included current as well as ex-smokers. Nonsmokers were all men who had never regularly smoked cigarettes for even 1 year, and pipe and cigar smokers were included in this group. A total of 4,706 men were identified. The mortality ratio for CHD was 1.6 (60 percent excess CHD mortality) in smokers as compared with nonsmokers.

San Francisco longshoremen were studied by Paffenbarger et al. (*205*); 3,686 men aged 35 to 74 were examined in 1951 and followed for 22 years. A total of 1,270 deaths were observed during 55,635 person-years of observation. After adjusting for difference in age, systolic blood pressure, and level of activity, the CHD mortality ratio for those smoking 20 cigarettes or more per day was 2.09 relative to those subjects who smoked fewer cigarettes or none.

Gillum and Paffenbarger reported CHD mortality from followup of 13,728 university students examined between 1939 and 1950 (*77*). CHD morbidity followup was observed in 8,852 who had returned self-administered questionnaires in 1962, 1966, or 1972. Four control subjects were randomly assigned to each of the 98 cases of fatal CHD, 78 cases of myocardial infarction, and 49 cases of angina pectoris. Fatal CHD, MI, and angina pectoris were strongly associated with smoking history; relative risks were near 2.5. Association with fatal CHD, or with MI, or both, was also apparent for a family history of CHD, weight, height, and systolic blood pressure.

The Canadian Department of National Health and Welfare initiated a study in 1955 of smoking and health in disability pensioners, principally veterans of World Wars I and II. Best reported the results of a 6-year followup in 1966 (*17*). The 78,000 Canadian men were aged 30 to 90 at the onset of the study. Smoking habits were determined at the start of the study. Nonsmokers were respondents who had never smoked. Ever smokers were those who had smoked at least 100 cigarettes during their lifetime or 10 cigars or 20 pipefuls of tobacco. Current smokers were those who reported smoking at the start of the study. Ex-smokers were those who had smoked previously, but had stopped smoking at the start of the study. During the 6-year followup, 9,491 deaths were observed, of

TABLE 9.—Coronary heart disease mortality ratios and rates, by age and smoking habit, prospective studies

Study	Mortality ratio and (rate)[1] by age				
ACS 25-State	35–44	45–54	55–64	65–74	75–84
Male nonsmoker	1.00(—)[2]	1.00(150)	1.00(542)	1.00(1400)	1.00(3132)
Male smoker	— (148)	2.81(422)	1.84(996)	1.45(2025)	1.24(3871)
Female nonsmoker	1.00	1.00(33)	1.00(163)	1.00(653)	1.00(1973)
Female smoker	—	2.00(66)	1.69(275)	1.44(941)	1.19(2349)
U.S. veterans	35–44	45–54	55–64	65–74	75–84
Nonsmoker or occasional only	1.00(18)	1.00(50)	1.00(501)	1.00(1015)	1.00(2216)
Cigarettes only	4.44(80)	7.00(353)	1.80(880)	1.60(1659)	1.20(2683)
Japanese in 29 health districts	40–49	50–59	60–69	70+	
Male nonsmoker	1.00(8.0)	1.00(48.3)	1.00(105.5)	1.00(189.6)	
Male smoker	3.09(24.7)	1.42(68.8)	1.62(170.7)	1.71(323.8)	
Female nonsmoker	1.00(6.1)	1.00(23.6)	1.00(79.5)	1.00(109.4)	
Female smoker	1.46(8.9)	1.75(41.2)	1.54(122.5)	1.44(157.9)	
ACS 9-State	50–54	55–59	60–64	65–69	
Nonsmoker	1.00(271)	1.00(431)	1.00(733)	1.00(1247)	
Smoker	1.92(521)	1.85(801)	1.66(1219)	1.41(1759)	
British physicians, male		<65		≥65	
Nonsmoker		1.00(189)		1.00(1655)	
Current, cigarettes only		2.19(413)		1.37(2259)	
British physicians, female					
Nonsmoker		1.00(31)		1.00(511)	
Smoker 1–14 cigarettes		1.41(44)		0.78(402)	
15–24 cigs		2.54(79)		2.18(1117)	
25+ cigarettes		2.74(85)		2.76(1411)	
Canadian veterans	55–59	60–64	65–69	70–74	75–79
Nonsmoker	1.00	1.00	1.00	1.00	1.00
Cigarettes only	1.90	1.61	1.38	1.79	1.45
Swedish prospective	18–39	40–49	50–59	60–69	
Nonsmoker	1.00	1.00	1.00	1.00	
Male smoker, cigs only	—	2.60	1.70	1.70	
Female smoker	—	—	2.60	1.10	
Swiss physicians	35–54	55–65	66–74	75+	
Nonsmoker	1.00	1.00	1.00	1.00	
Heavy smoker[3]	2.30	2.20	1.90	1.00	
California males in 9 occupations	35–44	45–54	55–64	65–69	
Nonsmoker	1.00	1.00	1.00	1.00	
Smoker	6.24	2.95	1.56	1.24	

[1] Rate per 100,000, unless otherwise stated.
[2] Number of deaths too small to compute a ratio.
[3] Heavy smoker: one or more packs per day.

which approximately 2,000 were attributed to coronary heart disease. Smokers experienced a death rate 68 percent higher than

that of nonsmokers. The excess mortality was due mainly to cardiovascular disease, with coronary heart disease alone accounting for 36 percent of the excess. The death rate due to coronary heart disease in smokers was 60 percent higher than the death rate in nonsmokers (Table 8).

In 1951, a study of mortality in British physicians was initiated. The results were reported by Doll and Hill (*44*) and subsequently by Doll and Peto (*45*) and by Doll et al. (*43*). A total of 34,400 men responded to the questionnaire (69 percent response rate). Followup questionnaires were sent in 1957, 1966, and 1972. Twenty-year mortality through October 1971 was reported in 1976 (*45*). Virtually all of the sample had been traced, and 10,072 deaths were identified. Nonsmokers were defined as those who had never smoked as much as one cigarette per day for as long as 1 year. Smoking status was updated using the information from followup questionnaires. Coronary heart disease accounted for 3,191 of the deaths. Information from the first questionnaire was related to the deaths occurring in the first 7 years, information from the second questionnaire to deaths in the next 8 years, and information from the third questionnaire was related to deaths in the last 5 years of the followup period. The death rate for smokers of all forms of tobacco was 37 percent higher than the death rate for nonsmokers.

Results of the 22-year mortality followup of female British physicians were reported recently (*43*). Among 6,194 respondents there were 1,094 deaths. Coronary heart disease was the underlying cause of death in 179. Among smokers, excess mortality was observed only for those smoking 15 or more cigarettes per day, but for these women the relative risks exceeded 2. The coronary heart disease mortality of all female smokers was only 35 percent of that of all male smokers. Those women who smoked more heavily (15 or more cigarettes per day) experienced CHD mortality that was 67 percent of that of men who smoked more than 15 cigarettes per day. Further analyses indicated that these female smokers had a lower cumulative smoking exposure than the male smokers; the female smokers had begun smoking at later ages and smoked fewer cigarettes, and fewer reported inhaling cigarette smoke. The CHD deaths among the female smokers were too few for more detailed analysis of the risk at levels of smoking behavior comparable to the most intense male smokers.

Examinations were given and questionnaires administered to 18,403 British civil servants working in London (*105*). Blood pressure, plasma cholesterol, blood glucose, height, weight, and relevant data were collected in a standardized fashion. During the 10-year followup there were 1,657 deaths, of which 704 were due to coronary heart disease. Grade of employment was significantly related to death from coronary heart disease; those at the highest grades

(administrators and professionals) experienced the lowest rates. However, at each grade of employment cigarette smokers experienced higher mortality than nonsmokers. The mortality of ex-smokers was similar to that of nonsmokers.

Grundy (*89*) reported the relationships of smoking habit and worksite exposure to carbon monoxide for 4,924 steelworkers in Ebbwvael, Wales, who were examined in 1964. After 10 years, 99 percent of the population surveyed was traced and 740 deaths were recorded. The total mortality and CHD mortality were higher than average for England and Wales. The smokers (73 percent of the sample) experienced a coronary heart disease mortality that was 80 percent higher (relative risk 1.8) than that of nonsmokers. Occupational exposure to carbon monoxide appeared to play a negligible role, in comparison with the importance of cigarette smoking, for coronary heart disease mortality. The high smoking rate in this population explained a substantial part of the excess mortality of this population compared with the average mortality for England and Wales.

In 1963, a probability sample of Swedish men and women aged 18 to 69 was surveyed by Cederlof et al. (*31*), and mortality was observed during the subsequent 10 years through December 1972. There were 25,444 male respondents (93 percent) and 27,342 female respondents (95 percent). In 1969, a followup questionnaire of a subsample indicated that smoking habits had not changed substantially since 1963 in the majority of those surveyed; for example, 78 percent of men and 63 percent of women who reported smoking 16 or more cigarettes per day in 1963 reported the same cigarette habit in 1969. During the 10-year followup, a total of 5,655 deaths were ascertained. Overall coronary heart disease mortality was 70 percent higher in male cigarette smokers and 30 percent higher in female cigarette smokers than in nonsmokers (Table 8). The possibility of confounding by other factors was evaluated. For univariate analysis, lower income and listing with the Swedish Alcohol Registry were associated with significantly higher CHD mortality. (In Sweden, violators of laws related to the use of alcohol, e.g., public drunkenness, drunk driving, illegal alcohol sales, are required to be registered.) However, cigarette smokers in each of these groups had significantly higher CHD mortality than never smokers, and the differences were particularly marked at higher levels of cigarette consumption. The CHD relative risks were also significantly higher for cigarette smokers within the high income group, among rural residents, and among those not listed in the Alcohol Registry.

In the Stockholm prospective study, risk factors for ischemic heart disease were evaluated in 3,486 men and 2,738 women who were first examined in 1961 through 1962 (*22*). During a 14 1/2-year followup, a total of 694 deaths were observed, of which 48 percent in men and

31 percent in women were attributed to ischemic heart disease. Of 235 ischemic vascular deaths in men, 189 were attributed to myocardial infarction. In univariate and multivariate analyses, cigarette smoking was significantly and independently related to the risk of ischemic vascular death in both sexes.

In 1955, a survey on the smoking habits of 3,749 Swiss physicians was initiated. The first reported findings (*252*) after 9 years of observation were similar to the findings in the British physicians study of Doll and Hill (*44*). More recently published data, based on 18 years of followup (*90*), recorded 1,212 deaths among those physicians who completed questionnaires during the original survey and for whom complete information concerning cause of death was available. A total of 280 coronary heart disease deaths (59 nonsmokers and 221 smokers) were reported. CHD mortality ratios increased with increasing number of cigarettes per day. Light smokers (10 or fewer cigarettes per day) had a mortality ratio of 1.33, increasing to 2.18 with the heaviest amount smoked (35 or more cigarettes per day). Mortality for CHD among smokers tended to be greater in the younger age groups than in the older age groups.

Hirayama has reported followup at 8, 10, and 13 years for 122,261 men and 142,857 women over 40 years of age who were residents in 29 health districts in Japan (*111–116*). There was an overall 95 percent participation rate, and ascertainment of cause of death was virtually 100 percent. In the 13-year followup, over 3 million person-years of risk and 39,127 deaths (22,946 in men and 16,181 in women) were observed. Heart disease was certified in 3,351 men and 2,651 women. At the time of the baseline survey, the proportion of smokers was 76 percent in men and 10.5 percent in women. Mortality ratios for smokers were 1.7 for men and 1.8 for women. The possibility of confounding by other factors was evaluated through cross-classification of smoking by social class, consumption of meat and milk, and alcohol consumption. Higher coronary heart disease mortality was observed with higher social class and among those consuming more meat and milk. Alcohol intake was inversely related to coronary heart disease mortality. At both high and low levels of these characteristics, however, the risk of death from CHD among smokers remained higher than among nonsmokers. The proportion of coronary heart disease mortality attributed to cigarette smoking in this population was 34.3 percent for men and 9.5 percent for women.

CHD mortality, as well as CHD incidence, is clearly much higher in cigarette smokers than in nonsmokers. This excess mortality occurred uniformly in each of the major prospective studies. It also occurred in populations of markedly different ethnic background and geographical location. The relationship also persisted when a number of other confounding variables were taken into account. The risk was somewhat lower for women, but in those groups of women

whose smoking habits approximated those of men, the CHD death rates were much closer to those of men.

Impact of Cigarette Smoking on Coronary Heart Disease Mortality With Increasing Age

Coronary heart disease mortality increases with increasing age in both cigarette smokers and nonsmokers. The question of the magnitude of the CHD risk due to smoking for different age groups is one that has important public health impact for advising individuals at different ages about the risks of smoking and the benefits of cessation. In several of the prospective mortality studies, the question of the magnitude of the risk of dying of coronary heart disease at different ages in smokers and nonsmokers has been examined.

Table 9 details the coronary heart disease death rates and mortality ratios for different age groups of smokers and nonsmokers in each of the prospective studies reporting these data. As can be seen from this table, the CHD mortality ratios for cigarette smokers compared with nonsmokers decline with increasing age. However, the decline in the ratio is the result of the rapid rise in CHD mortality rates with age in nonsmokers, and the absolute difference between the death rates of cigarette smokers and nonsmokers increases with increasing age. Thus, the excess risk is actually numerically greater in older populations than in younger populations, and the reduction in mortality ratio is an artifact of the fact that coronary heart disease is responsible for such a large part of the mortality of the older age groups in the United States.

Figures 11 (men) and 12 (women) present the relationships of CHD mortality and age for nonsmokers and smokers of various number of cigarettes per day. The risk for the nonsmoker increases steadily with increasing age, but with each increment in number of cigarettes smoked per day, there is a clear increase in CHD risk prior to age 70. The shape of the curve with increasing age remains similar with increasing number of cigarettes smoked per day, and the net effect is consistent with cigarette smoking increasing the apparent "CHD risk age" of the individual by 5 to 15 years.

The decline in the mortality ratio with increasing age found in the prospective mortality studies is consistent with the risk factor relationships found in the incidence studies. In these studies, cigarette smoking is responsible for a relatively larger proportion of the coronary heart disease occurring in younger populations and a smaller percentage of the total coronary heart disease occurring in older populations.

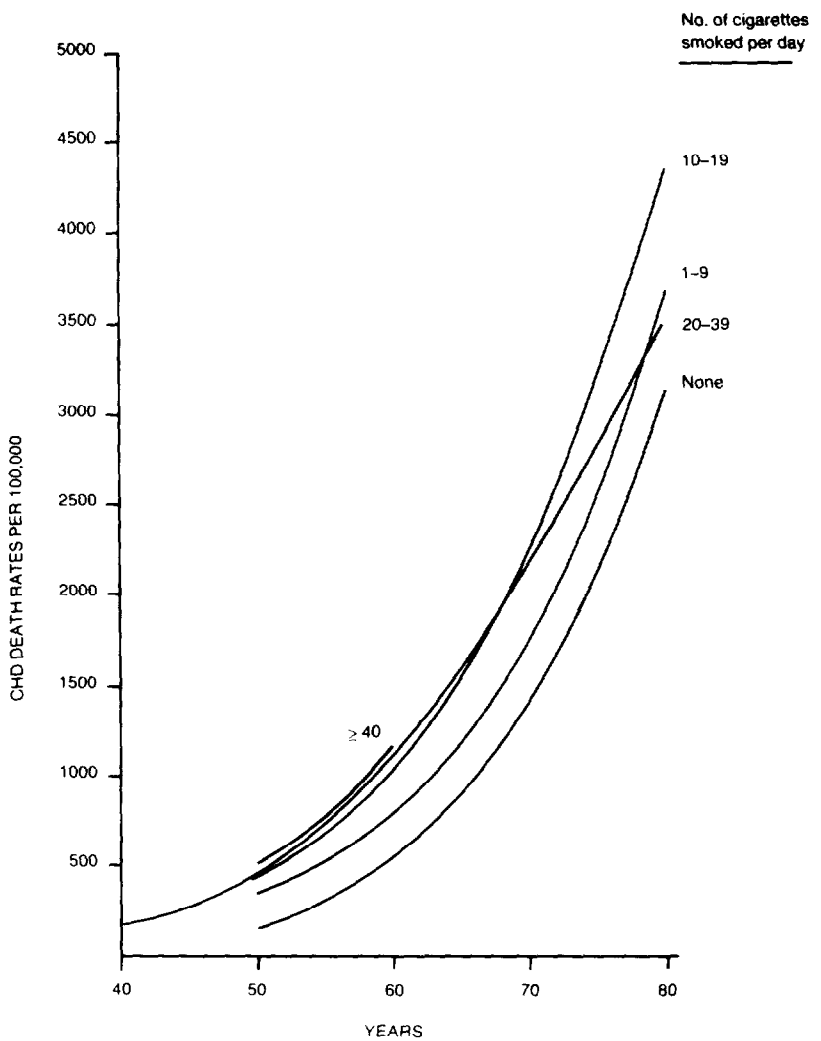


FIGURE 11.—CHD death rates (per 100,000), by age and number of cigarettes smoked per day, males

SOURCE: Derived from the ACS 25-State study (*93*).

Dose–Response Relationships

The large number of deaths observed in the prospective mortality studies allow a detailed examination of the relationship between the "dose" of smoke exposure and subsequent coronary heart disease mortality. The simplest measure of dose is the number of cigarettes smoked per day; however, the dose of smoke received by a person

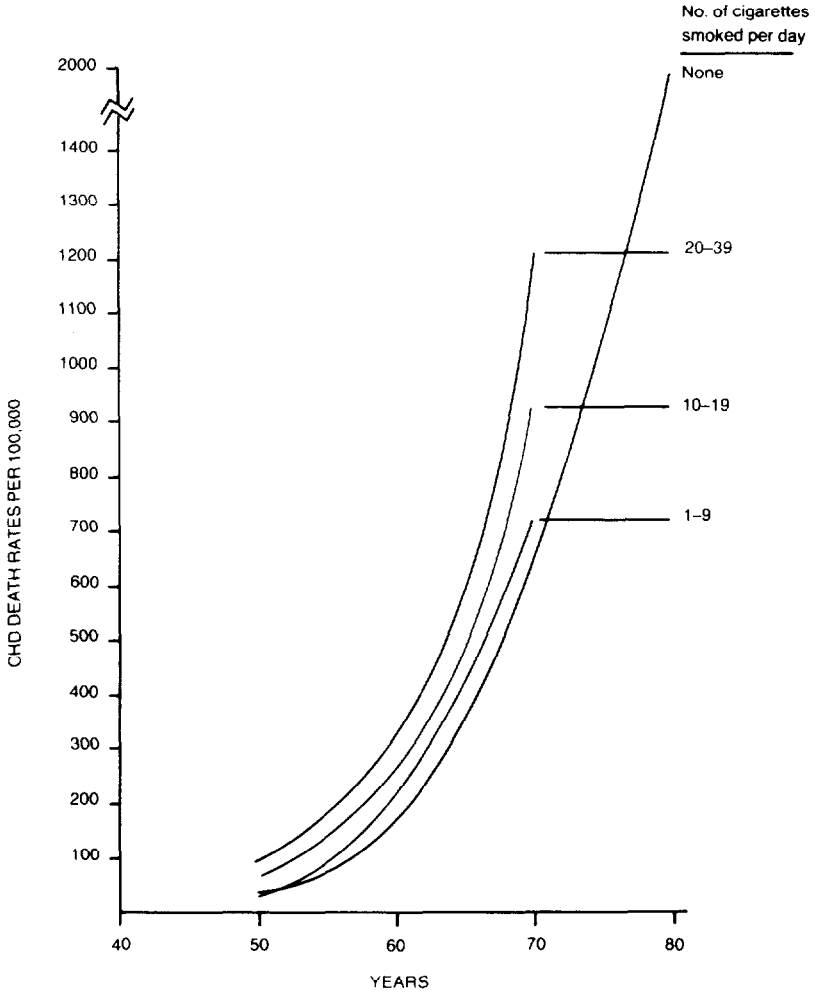


FIGURE 12.—CHD death rates (per 100,000), by age and number of cigarettes smoked per day, females

SOURCE: Derived from the ACS 25-State study (93).

would also be increased in those persons who inhaled deeply compared with those individuals who did not. The duration of the cigarette habit is also a measure of the dose of exposure; those persons who began to smoke earlier in life would have a greater cumulative exposure to cigarette smoke at any given age than those persons who began to smoke later in life. Several of the major prospective studies have examined these questions; the data are

TABLE 10.—Coronary heart disease mortality ratios by inhalation characteristic, prospective studies

Study	Sex	Age	Nonsmoker	Inhalation characteristic		
				Deep	Light	None
Swedish	Male		1.00	1.8	1.6	1.2
	Female		1.00	1.6	1.2	1.7[1]
				Yes		No
British physicians	Male	<65	1.00	2.2		1.4
		>65	1.00	1.5		1.3
				None–slight		Moderate–deep
ACS 25-State	Male	45–54	1.00	2.67		3.17
		55–64	1.00	1.83		2.01
		65–74	1.00	1.31		1.63
		75–84	1.00	1.29		1.20
	Female	45–54	1.00	1.82		2.15
		55–64	1.00	1.61		1.89
		65–74	1.00	1.30		1.78
		75–84	1.00	1.13		—[2]

[1] Number of deaths too small for statistical reliability.
[2] Number of deaths too small to compute.

presented in Tables 10, 11, and 12. Table 13 provides data from two studies that examined the risk of coronary heart disease mortality by length of time smoked. In general, they show that the more total years of smoking exposure the greater the overall risk of CHD mortality.

In the study of Canadian veterans, a progressive dose–response relationship was observed with number of cigarettes smoked per day. The CHD mortality ratio increased from 1.55 in those smoking 1 to 9 cigarettes per day to 1.78 among those who reported smoking 20 or more cigarettes per day. A similar relationship was found in the American Cancer Society 9-State study, where the excess CHD mortality rate varied from 29 percent in smokers of 1 to 9 cigarettes per day to 140 percent in smokers of 41 cigarettes or more per day.

In the American Cancer Society 25-State study, the number of CHD deaths was large enough to conduct a detailed examination of the relationship between the dose of cigarette smoke exposure and the subsequent coronary heart disease mortality. The mortality ratios for males in the group 45 to 54 years of age increased from 2.35 in those who smoked 1 to 9 cigarettes per day to 3.35 in those who smoked 40 or more cigarettes per day. In the next oldest age group, those 55 to 64 years of age, the mortality ratio increased from 1.54 in those who smoked 1 to 9 cigarettes per day to 2.13 in those who smoked 40 or more cigarettes per day (Table 14). The mortality ratio also increased with depth of inhalation. In the 45- to 54-year-old

TABLE 11.—Coronary heart disease mortality ratios by age began to smoke, prospective studies

Study	Age	Nonsmoker ratio	Smoker Mortality ratio by age of initiation			
U.S. veterans			≤14	15–19	20–24	≥25
	55–64	1.00	1.96	1.84	1.65	1.56
	65–74	1.00	2.03	1.66	1.54	1.55
ACS 25-State			≤14	15–24		≥25
Males	45–54	1.00	3.47	3.11		2.37
	55–64	1.00	2.08	1.99		1.70
	65–74	1.00	1.54	1.62		1.17
Females	45–54	1.00	—[1]	2.03		2.00
	55–64	1.00	—	1.64		1.74
	65–74	1.00	—	—		1.36
Japanese			≤14	15–19		≥20
Males		1.00	3.65	1.90		1.67
Swedish			≤16	17–18		≥19
Males		1.00	1.90	1.70		1.70
Females		1.00	2.00	1.10		1.30

[1] Number of deaths too small to calculate ratio.

age group, the mortality ratio increased from 2.67 in those who inhaled not at all or only very slightly to 3.17 in those who inhaled moderately or deeply (Table 10). There was also a consistent dose–response relationship when the age at which the individual started smoking was considered. The younger the age at which regular smoking began, the greater the mortality ratio. In the 45–54 age group the mortality ratio increased from 2.37 in those who began smoking at age 25 or older to 3.47 in those who began smoking prior to age 15 (Table 11).

For women, the excess mortality in the American Cancer Society 25-State study generally paralleled the dose–response relationship observed in men, but the CHD deaths were too few for evaluation of the risk related to the age at which smoking was begun.

A similar relationship was demonstrated in the study of California men in various occupations. The mortality ratio increased from 1.39 for those men who smoked half a pack per day to 1.74 for those who had smoked 1 1/2 packs or more per day. Mortality ratios increased with the duration of smoking from 1.05 in those who had smoked from 1 to 9 years to 1.77 in those who had smoked 20 years or more.

The study of British physicians also examined the question of a dose–response relationship. They found a steady increase in CHD mortality with increasing number of cigarettes smoked per day. The death rate from ischemic heart disease increased from 501 per 100,000 in those who smoked 1 to 14 cigarettes per day to 677 per

TABLE 12.—Coronary heart disease mortality ratios by amount smoked, prospective studies

Study	Males		Females	
	Cigs/day	Ratio	Cigs/day	Ratio
U.S. veterans	Nonsmoker	1.00		
	1–9	1.24		
	10–20	1.56		
	21–39	1.76		
	40+	1.94		
ACS 9-State	Nonsmoker	1.00		
	1–9	1.29		
	10–20	1.89		
	21–40	2.15		
	41+	2.41		
Japanese	Nonsmoker	1.00	(For female data, see Table 9)	
	1–14	1.59		
	15–24	1.79		
	25–49	2.11		
	50+	2.82		
ACS 25-State	Nonsmoker	1.00	(For female data, see Tables 9 and 14)	
	1–19	1.90		
	20+	2.55		
Canadian veterans	Nonsmoker	1.00		
	1–9	1.55		
	10–20	1.58		
	21+	1.78		
British physicians	Nonsmoker	1.00	Nonsmoker	1.00
	1–14	1.47	1–14	0.96
	15–24	1.58	15–24	2.20
	25+	1.92	25+	2.12
Swedish	Nonsmoker	1.00	Nonsmoker	1.00
	1–7	1.50	1–7	1.20
	8–15	1.70	8–15	1.60
	16+	2.20	16+	3.00
California occupations	Nonsmoker	1.00		
	about 1/2 pk	1.39		
	about 1 pk	1.67		
	about 1 1/2 pk	1.74		
Swiss physicians	Nonsmoker	1.00		
	1–10	1.33		
	10–19	1.42		
	29–34	1.77		
	35 or more	2.18		

100,000 in those who smoked 25 or more cigarettes per day. Depth of inhalation was analyzed after adjusting for age and amount smoked. Those responding that they did inhale experienced a 57 percent higher mortality rate than those responding that they did not inhale.

A dose–response relationship was also reported in the U.S. veterans study, the study of mortality in northeast England, the

TABLE 13.—Coronary heart disease mortality ratios by number of years having smoked, prospective studies

Study	Nonsmoker	Number of years having smoked							
		<5	5–9	10–14	15–19	20–29	30–39	≥40
Canadian veterans	1.00	1.4	1.7	1.5	1.7	1.6	1.5	1.6
		1–9		10–19			20+	
California occupations	1.00	1.05		1.13			1.77	

TABLE 14.—Coronary heart disease mortality ratios, males and females, by age and amount smoked, ACS 25-State study

Number of cigarettes/day	Age							
	45–54		55–64		65–74		75–84	
	M	F	M	F	M	F	M	F
Nonsmoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1–9	2.35	9.94	1.54	1.26	1.26	1.10	1.17	—[1]
10–19	3.09	2.00	1.92	1.64	1.61	1.42	1.39	—
20–39	3.11	2.67	2.04	2.01	1.56	1.85	1.11	—
40+	3.35	—	2.13	—	—	—	—	—

[1] Number of deaths too small to compute.

Swedish probability sample study, the Stockholm prospective study, and the study of 29 health districts in Japan. Mortality from CHD in the Whitehall study was higher in inhalers than in noninhalers, but the relative risk was reduced after adjusting for cigarette consumption and tar yield. Among inhalers, the risk increased with the amount smoked; this trend was less evident in those not inhaling.

Thus, in those studies that have had an adequate number of deaths to examine the question of a dose–response relationship between cigarette smoking and death from coronary heart disease, a clear dose–response relationship has been demonstrated for the number of cigarettes smoked per day, depth of inhalation, age at initiation of the smoking habit, and total duration of the smoking habit. The risk of coronary disease mortality is lower with fewer cigarettes smoked per day, but the evidence presented in the prospective mortality studies does not suggest a threshold for this effect. There is no evidence to suggest that any level of cigarette smoking is safe with regard to coronary heart disease risk.

Low Tar and Nicotine Cigarettes

There has been a major change in the tar and nicotine yield of the cigarettes being smoked by the U.S. population over the last 30 years. The impact of this decline in tar and nicotine yield on the risk of developing coronary heart disease in individuals smoking lower yield cigarettes has been examined in detail in the 1981 Report of the Surgeon General *The Health Consequences of Smoking: The Changing Cigarette* (*262*). There are essentially no epidemiological data on the risk of very low yield cigarettes (those below 5 mg of tar). The American Cancer Society 25-State study did, however, address the relative risk of those who smoked cigarettes with varying yields of tar (*95*). Groups were matched for age, race, number of cigarettes smoked per day, age at which smoking began, place of residence, occupational exposures, education, and history of lung cancer or heart disease. CHD mortality was calculated for two 6-year periods (1960–1966 and 1966–1972) for those smoking low, medium, or high tar and nicotine cigarettes. The men and women (both in early and late periods) who smoked cigarettes with high tar and nicotine yield experienced higher CHD death rates than those who smoked low tar and nicotine cigarettes (Table 15). Additional analyses were performed after further matching of the groups with respect to history of stroke; diabetes mellitus; hypertension; usual amount of exercise; obesity; consumption of aspirin, tea, coffee, and alcohol; and occupation. Although this procedure resulted in fewer matched subjects, the results were comparable to the analyses above; CHD mortality in the low tar and nicotine cigarette smokers was 86 percent of that of the high tar and nicotine cigarette smokers. However, this slight reduction in CHD mortality associated with smoking low tar and nicotine cigarettes disappeared if an increase in the number of cigarettes smoked per day occurred. Those smokers of low tar and nicotine cigarettes who smoke between 20 and 30 cigarettes per day experienced a 10 percent higher coronary heart disease mortality than did smokers of 1 to 19 high tar and nicotine cigarettes. In addition, a comparison of matched subjects who never smoked regularly with those who smoked low tar and nicotine cigarettes revealed that the low tar and nicotine cigarette smokers experienced a 66 percent higher coronary heart disease mortality rate.

Data from the Framingham study on the incidence of coronary heart disease (*30*) have not shown a lower CHD risk among filter smokers compared with nonfilter smokers.

Data from the Whitehall study have been published that examine tar yield by number of cigarettes smoked per day in inhalers and noninhalers for CHD mortality. This is presented in Table 16. While no clear pattern is evident for noninhalers, among inhalers there was a tendency for the highest CHD rates to be seen in those smoking cigarettes with the highest tar yield (*108*). In a recent study

TABLE 15.—Adjusted number of coronary heart disease deaths and mortality ratios during each of two periods of time, by sex and by tar and nicotine content of cigarettes usually smoked

Sex	Period[1]	High tar and nicotine	Medium tar and nicotine	Low tar and nicotine
		Adjusted number of CHD deaths		
Male	1	696.5	632.5	645.6
Male	2	336.0	345.6	274.2
Female	1	318.7	277.5	257.4
Female	2	265.6	228.0	215.5
Total		1,616.8	1,483.3	1,392.7
		Mortality ratios		
Male	1	1.00	0.91	0.93
Male	2	1.00	1.03	0.82
Female	1	1.00	0.87	0.81
Female	2	1.00	0.86	0.81
Total		1.00	0.92	0.86

[1] Period 1: 1960–1966; Period 2: 1966–1972.
SOURCE: Hammond et al. (95).

TABLE 16.—Ten-year coronary heart disease mortality per hundred (and number of deaths) standardized for age and employment grade, according to cigarette consumption and tar yield, Whitehall study

	Inhalers						Noninhalers					
	1–9/day		10-19/day		≥20/day		1-9/day		10–19/day		≥20/day	
Tar (mg/cig)	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.
18–23	2.68	(14)	5.63	(71)	6.60	(101)	3.94	(14)	4.91	(17)	6.05	(20)
24–32	3.81	(7)	6.57	(30)	6.23	(36)	1.78	(3)	9.03	(10)	4.27	(6)
≥33	7.42	(23)	6.47	(37)	7.84	(10)	5.08	(4)	4.75	(4)	0.00	(0)
Total	4.29	(44)	5.98	(138)	6.56	(147)	3.48	(21)	5.73	(31)	5.18	(26)

NOTE: Rate for lifelong nonsmokers of cigarettes = 2.75 (70).
SOURCE: Higgenbottam et al. (*106*).

(*140*), tar and nicotine content of the cigarettes was documented; those men who smoked low yield cigarettes did not have a lower risk for myocardial infarction than those smoking higher yield cigarettes.

The relative risk of developing coronary heart disease in persons smoking low yield cigarettes and persons smoking high yield cigarettes is further confounded by the possibility that those who

TABLE 17.—Coronary heart disease mortality ratios for male cigarette, pipe, cigar, and mixed pipe and/or cigar smokers, prospective studies

Study	Mortality ratios				
	Nonsmoker	Cigarette smoker	Pipe smoker	Cigar smoker	Mixed pipe and/or cigar smoker
U.S. veterans[1]	1.00	1.58	1.02	1.12	
ACS 9-State	1.00	1.70	—	1.28	
Swedish	1.00	1.70	1.40		
ACS 25-State[2]	1.00	1.90–2.55	1.08		
British physicians	1.00	1.62			1.03

[1] Smoker groups are "pure" smokers only.
[2] Age 55–84 only.

smoke low yield cigarettes may smoke greater numbers of cigarettes per day or may alter the manner in which they smoke those cigarettes to increase the yield from the cigarette. The available data are conflicting concerning a possible reduction in risk of CHD for those smoking the lower yield cigarettes; further evidence is needed before this question can be definitively answered.

Pipe and Cigar Smoking

A number of studies have addressed the question of the relative risk for CHD from smoking pipes and cigars compared with cigarettes. Those prospective mortality studies containing data that address this question are presented in Table 17. In general, the risk for coronary heart disease mortality of smoking pipes and cigars is substantially lower than the risk of smoking cigarettes. This is generally felt to be due to the tendency of pipe and cigar smokers not to inhale smoke into the lung. If this is the mechanism of this lower risk, then the tendency of those who switch from cigarettes to pipes and cigars to continue to inhale the smoke may minimize or eliminate the reduction in risk for coronary heart disease that might be expected after switching to pipes and cigars from cigarettes.

Cessation

Whether the excess coronary heart disease mortality that occurs with cigarette smoking decreases over time following cessation of cigarette smoking is a question of great importance for those individuals who are currently smoking cigarettes. Data from the prospective mortality studies that have examined this question are presented in Table 18.

TABLE 18.—Cessation of smoking and coronary heart disease mortality ratios, prospective studies

Study	Continuing smoker		Ex-smoker	
U.S. veterans	1.58		1.16	
Swedish males	1.70		1.50	
females	1.30		1.50	
ACS 25-State	1-19[1]	20+	1-19	20+
males	1.87	2.05	1.26	1.62
Canadian veterans	1.60		1.46	
British physicians males	1.62		1.29	
Japanese males in 29 health districts	1.71		1.34	

[1] Number of cigarettes smoked daily.

TABLE 19.—Cessation of smoking and CHD mortality ratios, by length of time off cigarettes and number of cigarettes smoked daily, ACS 25-State study, 6-year followup

Years stopped smoking	Amount smoked per day	
	1-19	20+
None, current smoker	1.87	2.05
Less than 1	2.00	2.13
1-4	1.43	2.00
5-9	1.44	1.45
10 or more	0.99	1.35
All ex-smokers	1.26	1.62

In the American Cancer Society 25-State study, the mortality ratios in former smokers compared with continuing smokers were progressively lower with increasing intervals of smoking cessation. For those who had smoked less than 20 cigarettes per day, the CHD mortality after 10 years of cessation was comparable with that of those who had never smoked regularly. However, for those who had smoked 20 or more cigarettes per day, the CHD mortality rate remained 35 percent higher even after 10 years (Table 19).

The British study of physicians also conducted a detailed analysis of the effects of cessation. The relative risk for males 30 to 54 years of age was 1.9 for those who had discontinued smoking for less than 5 years, but it was 1.3 for those who had discontinued smoking for 5 or more years. Those who discontinued smoking for 15 years or more had a relative risk that remained slightly above 1. Those aged 30 to

TABLE 20.—CHD mortality ratios by length of time off cigarettes

Study	Age	Mortality ratios: Nonsmoker	Years off cigarettes				Comments
			<5	5–9	10–14	5+	
British physicians (20-yr followup)	30–54	1.00	1.9	1.3	1.4	1.3	
	55–64	1.00	1.9	1.4	1.7	1.3	
	65+	1.00	1.0	1.3	1.2	1.1	
			<10		>10		
Swedish males (10-yr followup)		1.00	1.50		1.00		
			≤4		≥5		
Japanese males in 29 health districts (13-yr followup)		1.00	1.15		0.90		Smokers who consumed <200,000 cigarettes/ lifetime
		1.00	2.10		1.82		Smokers who consumed >200,000 cigarettes/ lifetime

64 had a relative risk of 1.3 after 15 years, while those 65 and over had a relative risk of 1.1 (Table 20).

The Swedish national probability sample study examined former smokers who had stopped in the 10 years prior to 1963. A relative risk of 1.6 existed for those who had smoked 20 years or more prior to quitting, but the relative risk was 0.9 for those who had smoked less than 20 years before quitting. Those at younger ages had greater residual relative risks than those in the older age groups. Among those who had stopped smoking 10 or more years prior to the beginning of the study, no significant excess risk of coronary disease was observed. The results in women were consistent with those in men, but the cases were too few for detailed analysis (Table 20).

In the Japanese study of 26 health districts, former smokers exhibited relative risks that were related inversely to the time since smoking cessation; the residual risk was directly proportional to the number of cigarettes smoked prior to quitting.

Data from the 16-year followup of U.S. veterans provides information on CHD mortality for ex-smokers by the number of cigarettes smoked per day (Table 21). Those ex-smokers with the lowest smoking exposure levels as measured by the number of cigarettes consumed per day had the lowest CHD mortality ratios. When all ex-smokers were analyzed by the length of time since cessation (Figure 13), ex-smokers who had been abstinent for 20 or more years had a CHD mortality ratio virtually identical to lifelong nonsmokers (1.00 versus 1.05). Friedman et al. (*69*) found that the benefits of quitting

TABLE 21.—Cessation of smoking and CHD mortality ratios of current smokers versus ex-smokers, by number of cigarettes smoked daily, U.S. veterans study, 16-year followup

No. cig/daily	Current smoker	Ex-smoker
Nonsmoker	1.00	1.00
1–9	1.24	1.02
10–20	1.56	1.14
21–39	1.76	1.31
40+	1.94	1.30
All smokers	1.68	1.16

SOURCE: Rogot and Murray (*224*).

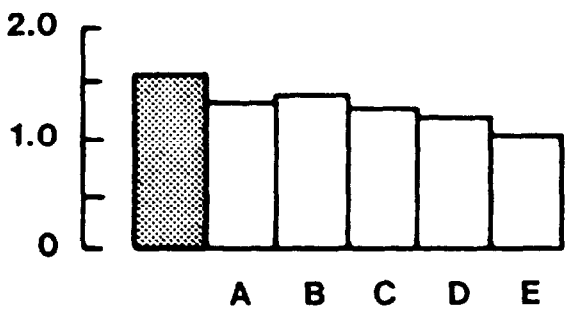


FIGURE 13.—Coronary heart disease mortality rates by number of years stopped smoking, U.S. veterans study, 16-year followup

NOTE: A = stopped less than 5 years; B = stopped 5–9 years; C = stopped 10–14 years; D = stopped 15–19 years; E = stopped 20 or more years.
SOURCE: Rogot and Murray (*224*).

smoking could not be explained by differences in other risk factor levels between continuing smokers and quitters.

Thus, cessation of cigarette smoking resulted in a reduction in the risk of CHD in each of the mortality studies that have examined the question. There appears to be some residual excess CHD risk in those ex-smokers who smoked heavily for extended periods of time prior to

quitting, and the magnitude of this residual risk is proportional to the total lifetime exposure to cigarette smoke.

Populations With Low Rates of Smoking

Mortality has been studied in several population groups that have abstained from cigarette smoking for religious reasons. These include Seventh Day Adventists in California, Mormons living in Utah, members of the Reorganized Church of Jesus Christ of the Latter Day Saints living in Missouri, and Old Order Amish living in Indiana, Ohio, and Pennsylvania.

Seventh Day Adventists in California prohibit the use of tobacco and alcohol and advocate a well-balanced diet that includes a relatively large grain and fruit content. As reported by Wynder and Lemon (*285*), the Seventh Day Adventists have experienced exceptionally low coronary heart disease as well as low cancer mortality.

Cardiovascular mortality from 1969 to 1971 in Mormons and non-Mormons living in Utah was studied by Lyon et al. (*165*). Utah has the lowest per capita consumption of cigarettes and alcohol of the 50 States, and this is attributable to the Mormon Church's position against the use of tobacco and alcohol. Below the age of 65, both Mormons and non-Mormons in Utah had significantly lower coronary heart disease mortality than the average for U.S. whites, but above the age of 65 only Mormons had significantly lower rates. Mormon men and women in comparison with non-Mormon men and women living in Utah experienced 25 percent and 29 percent fewer deaths, respectively, from coronary heart disease. The rates were lower in Mormons than in non-Mormons at all ages. Below the age of 65, Mormon men and women experienced CHD mortality rates only 66 percent and 51 percent, respectively, of the rates for coronary heart disease that were experienced by U.S. whites.

The mortality of Missouri residents who were members of the Reorganized Church of Jesus Christ of Latter Day Saints (RLDS) was compared with the mortality of other white Missouri residents and of Utah residents for the period 1971–1978 (*167*). The RLDS advocates abstinence from the use of tobacco, alcohol, and hot drinks. A well-balanced diet is recommended, with ample whole grains, fruits, and vegetables but with moderate intake of meat. The total mortality rate for Missouri RLDS residents was 22.6 percent lower than that of other Missouri white residents and 14.4 percent lower than that of Utah residents. CHD mortality was 17.4 percent lower than CHD mortality for other Missouri whites. The CHD mortality of RLDS members appears to be intermediate between that of Mormons living in Utah and that of U.S. whites.

Mortality among Old Order Amish living in Ohio (1960–1975), Indiana (1967–1972), and Pennsylvania (1970–1975) was reported by

Hamman et al. (*92*). This unique population group is rooted in a rural lifestyle reminiscent of 19th century America. Their diet has been incompletely characterized, but probably is relatively high in fats and carbohydrates. Tobacco use has been widespread among men, but principally limited to pipe and cigar smoking and tobacco chewing. Alcohol intake is thought to be limited to consumption at home, and excessive intake is uncommon. Mortality of the Amish was compared with mortality of the non-Amish residents in the study counties. The non-Amish residents included an unknown proportion of those who were former members of the Amish faith and members of other conservative religious groups who shared components of the Amish lifestyle. Amish men, but not women, 40 to 69 years of age had significantly lower total mortality (61 percent and 98 percent, respectively) and cardiovascular mortality (65 percent and 89 percent) than did the non-Amish residents living in the same counties. Lower cardiovascular disease mortality for the Amish men was highly significant in all three States.

Conclusions

1. Cigarette smoking is a major cause of coronary heart disease in the United States for both men and women. Because of the number of persons in the population who smoke and the increased risk that cigarette smoking represents, it should be considered the most important of the known modifiable risk factors for CHD.
2. Overall, cigarette smokers experience a 70 percent greater CHD death rate than do nonsmokers. Heavy smokers, those who consume two or more packs per day, have CHD death rates between two and three times greater than nonsmokers.
3. The risk of developing CHD increases with increasing exposure to cigarette smoke, as measured by the number of cigarettes smoked daily, the total number of years one has smoked, and the degree of inhalation, and with an early age of initiation.
4. Cigarette smokers have a twofold greater incidence of CHD than do nonsmokers, and heavy smokers have an almost fourfold greater incidence.
5. Cigarette smoking is a major independent risk factor for CHD, and it acts synergistically with other risk factors (most notably, elevated serum cholesterol and hypertension) to greatly increase the risk of CHD.
6. Women have lower rates for CHD than do men. In particular, CHD rates for women are lower prior to the menopause. A part of this difference is due to the lower prevalence of smoking in women, and for those women who do smoke, to the tendency to smoke fewer cigarettes per day and to inhale less deeply.

Among those women who have smoking patterns comparable to male smoking patterns, the increments in CHD death rates are similar for the two sexes.

7. Women who use oral contraceptives and who smoke increase their risk of a myocardial infarction by an approximately tenfold factor, compared with women who neither use oral contraceptives nor smoke.
8. Cigarette smoking has been found to significantly elevate the risk of sudden death. Overall, smokers experience a two to four times greater risk of sudden death than nonsmokers. The risk appears to increase with increasing dosage as measured by the number of cigarettes smoked per day and diminishes with cessation of smoking.
9. The CHD mortality ratio for smokers compared with nonsmokers is greater for the younger age groups than for the older age groups. Although the smoker-to-nonsmoker mortality ratio narrows with increasing age, smokers continue to experience greater CHD death rates at all ages.
10. Cigarette smoking has been estimated to be responsible for up to 30 percent of all CHD deaths in the United States each year. During the period 1965 to 1980 there were over 3 million premature deaths from heart disease among Americans attributed to cigarette smoking. Unless smoking habits of the American population change, perhaps 10 percent of all persons now alive may die prematurely of heart disease attributable to their smoking behavior. The total number of such premature deaths may exceed 24 million.
11. Cessation of smoking results in a substantial reduction in CHD death rates compared with those of persons who continue to smoke. Mortality from CHD declines rapidly after cessation. Approximately 10 years following cessation the CHD death rate for those ex-smokers who consumed less than a pack of cigarettes daily is virtually identical to that of lifelong nonsmokers. For ex-smokers who had smoked more than one pack per day, the residual risk of CHD mortality is proportional to the total lifetime exposure to cigarette smoke.
12. Epidemiologic evidence concerning reduced tar and nicotine or filter cigarettes and their effect on CHD rates is conflicting. No scientific evidence is available concerning the impact on CHD death rates of cigarettes with very low levels of tar and nicotine.
13. Smokers who have used only pipes or cigars do not appear to experience substantially greater CHD risks than nonsmokers.

Appendix: Prediction of CHD

The probability of developing CHD may be accurately predicted within populations that are stratified by risk scores based on daily use of cigarettes and the levels of the other major risk factors. This may be accomplished efficiently using the multiple logistic equation, which provides for simultaneous consideration of multiple risk factors (*40, 80, 84, 85, 88, 91, 126, 130, 133, 135, 137, 139, 143, 159, 168, 214, 221, 246*). Furthermore, the reproducibility of the relationship between risk factors and the subsequent development of CHD may be tested among different population samples. As demonstrated in the investigations cited above, the risk of CHD in white populations in the United States and northern Europe has been shown to be predictable based on a knowledge of cigarette smoking, blood pressure, and serum cholesterol. In other population groups with lower incidences of CHD, relative risk has been predicted well, although the magnitude of risk has been overestimated. Such predictability confirms the importance of the major risk factors to the development of CHD.

Pooling Project

The relationships among a number of characteristics measured at baseline examinations and the subsequent development of CHD was studied intensively in the Pooling Project, in which the experience of five major prospective studies of defined cohorts were compared and combined. From these analyses it was concluded that the levels of the three major risk factors—cigarette smoking, blood pressure (systolic or diastolic blood pressure), and serum cholesterol—accounted for most of the risk predicted by the variables considered; the other variables were relative weight and ECG abnormalities. Furthermore, the relationships of the risk factors to CHD were similar among the cohorts considered.

Ranking of Risk

On the basis of the observed relationships among the levels of the major risk factors and the subsequent incidence of CHD in the pooled data, the men in each of the cohorts could be ranked by order of expected risk. With the men thus ranked in quintiles of estimated risk from low to high, the incidence of CHD was found to be nine times higher for the men in the uppermost quintile than for the men in the lowermost quintile.

Generalizability

To test the generalizability of the relationship between these risk factors and the subsequent incidence of CHD (in other words, the prediction of future CHD events from given individual characteris-

tics), the multiple logistic equation describing the relationship of risk factors to subsequent events in the combined data from the cohorts contributing to the pooled data were applied to other cohorts. In the cohort of U.S. railroad men, there was good correspondence between the number of first major coronary events predicted and the numbers observed by quintile of risk; 45 percent of CHD events were observed in the highest quintile and 74 percent were observed in the upper two quintiles. The total number of estimated cases was 133 as compared with 112 actually observed in the cohort of U.S. railroad men (Table 22).

Comparability of Framingham Study Results With the Results in the Other Cohorts

The mathematical relationships between the risk factors and the subsequent incidence of CHD for the Framingham study men were near the averages observed for the other four cohorts in the Pooling Project (Tables 23 and 24). The Framingham study results have been compared with the results of other cohort studies in the United States and elsewhere (*25, 77, 85, 181*); therefore, it is of interest to consider in some detail the closeness of agreement between the prediction of CHD by Framingham data and by the other cohort data in the Pooling Project. In univariate analyses for each study by CHD event and risk factor, it was found that the Framingham coefficients were not significantly different from those of the other cohorts, except for a higher coefficient for serum cholesterol in the Tecumseh cohort and a higher coefficient for cigarette smoking in the Chicago Gas Company cohort (Table 23). The Framingham coefficient for smoking was slightly lower than the average for the other cohorts.

Risk Indices for Individual Use

Multivariate risk-scoring indices for estimating the risk of CHD based on daily use of cigarettes and the levels of other characteristics have been developed for prediction of the risk of CHD in individuals. These include RISKO, developed by the Michigan Heart Association, the Framingham Risk Index, based on the Framingham study experience, and the Self-Scoring Risk Test, based on the experience of the Chicago Western Electric Company cohort (*54, 138, 178*).

The discriminative power of RISKO and the Framingham Risk Index to identify individuals who would develop CHD was evaluated in the experience of Los Angeles County safety personnel (*256*). Personnel who were free of symptoms (4,066 individuals) were examined and followed in the 1971 to 1979 time frame with a less than 3 percent loss to followup (*256*). Subsequent to initial examination, 71 developed CHD; these symptomatic cases were characterized by a higher proportion of cigarette smokers (60 percent compared with 37 percent), higher systolic blood pressures, higher serum

TABLE 22.—Prediction of 10-year risk of a first event for men of two studies (Minnesota business and professional men and Minnesota-based railroad workers) from parameters of the multivariant logistic analysis for Pool 5, age 40–59 at entry

Quintiles of expected or predicted risk	Pool 5 (6,875 men)				Minnesota business and professional men (280 men)						Minnesota-based railroad workers (2,422 men)					
	Expected		Observed		Predicted		Predicted, corrected for duration of followup[1]		Observed		Predicted		Predicted, corrected for duration of followup[2]		Observed	
I	41.3[3]	30.0[4]	29	21.1	1.0	18.4	2.0	37.6	3	53.6	16.9	34.8	8.3	17.0	8	16.5
II	71.2	51.8	71	51.6	1.6	27.9	3.3	57.0	4	71.4	30.6	63.2	15.0	31.0	5	12.4
III	101.1	73.5	106	77.1	2.2	39.6	4.5	80.9	7	125.0	44.2	91.3	21.7	44.7	15	31.0
IV	145.5	105.8	164	119.3	3.1	55.3	6.3	113.0	6	107.1	64.7	133.7	31.7	65.5	33	68.2
V	264.0	192.0	251	182.5	5.5	97.4	11.2	199.1	12	214.3	115.2	237.0	56.4	116.1	50	102.9
All	623.1	90.6	621	90.3	13.4	47.7	27.4	97.5	32	114.3	271.5	112.1	133.0	54.9	112	46.2
V/I	6.4		8.7		5.3		5.3		4.0		6.8		6.8		6.3	
V–I	222.7	162.0	222	161.4	4.5	79.0	9.2	161.5	9	160.7	98.3	202.2	48.1	99.1	42	86.4
Percentage of events in V	42.4		40.4		40.8		40.8		37.5		42.2		42.4		44.6	
Percentage of events in VI + V	65.7		66.8		64.0		64.0		56.3		66.3		66.3		74.1	

[1] Mean duration of followup for Pool 5 men was sizably less than for Minnesota business and professional men. Since the relationship between age and incidence of major coronary events is curvilinear (exponential), not linear, a correction factor was derived from the 1970 U.S. life table for white men starting at age-predicted numbers of events; rates were multiplied by this correction factor—2,044—to obtain the numbers of events and rates for different duration of followup.

[2] Mean duration of followup for Pool 5 men was sizably greater than for Minnesota-based railroad workers. A correction factor—0.$\overline{899}$—was derived by the method described in the footnote above.

[3] Number of events.

[4] Rate per 1,000.

SOURCE: Pooling Project Research Group (*214*).

TABLE 23.—Standardized univariate logistic coefficients for deaths from myocardial infarction, CHD, and all causes, by study and risk factor

	Framingham	Albany	Chicago Gas	Chicago W.E.	Tecumseh
Myocardial infarction or CHD death					
SBP	0.3373	0.2695	0.3123	0.2511	0.5633
DBP	0.3126	0.2845	0.3169	0.2797	0.5059
Cholesterol	0.3433	0.3614	0.2685	0.3271	0.7501[1]
Relative weight	0.2775	0.2385	0.1496	0.0703	-0.0136
Smoking	0.3115	0.4450	0.6984[1]	0.3049	0.5183
Death all causes					
SBP	0.4671	0.4671	0.4102	0.4196	0.2926
DBP	0.3684	0.4006	0.2426	0.3382	0.4906
Cholesterol	0.1156	0.1321	0.1815	0.0796	0.4533[1]
Relative weight	0.0540	-0.1452	-0.0921	0.1645	-0.0214
Smoking	0.3876	0.3745	0.5806	0.3229	0.5546
CHD death					
SBP	0.4880	0.3103	0.3663	0.3212	0.5831
DBP	0.4139	0.3394	0.2818	0.4056	0.5518
Cholesterol	0.2872	0.2550	0.2474	0.2344	0.8586[2]
Relative weight	0.3229	0.0490	0.1967	0.0765	0.0453
Smoking	0.3327	0.4612	0.8060	0.2311	0.4623

[1] Differs significantly from Framingham ($p < .05$).
[2] Differs significantly from Framingham ($p < .01$).
NOTE: The coefficients here are given in less precision for ease of comparison. For each coefficient in the studies other than Framingham, a test statistic was calculated to test whether it differed significantly from the comparable coefficient for Framingham. Those that did were appropriately marked. The test statistic is the difference between the coefficients divided by the standard error of the difference. The standard error of the difference is calculated by taking the square root of the sum of the variance of the coefficients. Under appropriate normality assumptions, this statistic is a standard normal deviate.
SOURCE: McGee and Gordon (*168*).

cholesterol, slightly greater prevalence of excess body fat, and less frequent regular exercise. The risk scores of cases in comparison with noncases were significantly higher with RISKO and with the Framingham Risk Index. In stepwise discriminant analysis, the Framingham Risk Index and RISKO, separately and in combination, identified the group with elevated levels of risk factors that experienced a higher incidence of CHD than the group with low levels of the risk factors.

Blacks and Whites in Evans County, Georgia

In looking for an explanation of the large difference in CHD incidence rates between black and white men in the Evans County study (see above), the incidence at different levels of risk factors was evaluated (*28, 107, 258*). Although cigarette smoking and other risk factors were strongly related to the incidence, differences in baseline characteristics did not appear to explain the higher rates of CHD in white men. However, white and black sharecroppers and farm

TABLE 24.—Standardized multivariate logistic coefficients for deaths from myocardial infarction, CHD, and all causes, by study and specified set of risk factors

	Framingham	Albany	Chicago Gas	Chicago W.E.	Tecumseh
Myocardial infarction or CHD death					
SBP	0.3432	0.2426	0.3376	0.2342	0.5524
Cholesterol	0.2905	0.3534	0.2187	0.3056	0.7989[2]
Smoking	0.3374	0.4227	0.7010[1]	0.2820	0.5509
DBP	0.3022	0.2725	0.3694	0.2680	0.5222
Cholesterol	0.2893	0.3462	0.2176	0.2979	0.7705[1]
Smoking	0.3352	0.4359	0.7240[1]	0.2934	0.5647
Death all causes					
SBP	0.5483	0.4254	0.4495	0.275[1]	0.4742
Cholesterol	0.0209	0.0992	0.1307	0.0260	0.4617[1]
Smoking	0.4845	0.3453	0.6033	0.3206	0.5614
DBP	0.4305	0.3983	0.2855	0.3382	0.4971
Cholesterol	0.0279	0.0937	0.1339	0.0145	0.4391[1]
Smoking	0.4655	0.3638	0.6012	0.3372	0.5880
CHD death					
SBP	0.5292	0.2697	0.3936	0.2981	0.5720
Cholesterol	0.2033	0.2406	0.1881	0.2025	0.9164[2]
Smoking	0.4027	0.4107	0.8076	0.2092	0.4989
DBP	0.4200	0.3126	0.3304	0.3799	9.5752
Cholesterol	0.2088	0.2324	0.1903	0.1905	0.8918[2]
Smoking	0.3806	0.4273	0.8200	0.2273	0.5140

[1] Differs significantly from Framingham ($p < .05$).

[2] Differs significantly from Framingham ($p < .01$).

NOTE: The coefficients here are given in less precision for ease of comparison. For each coefficient in the studies other than Framingham, a test statistic was calculated to test whether it differed significantly from the comparable coefficient for Framingham. Those that did were appropriately marked. The test statistic is the difference between the coefficients divided by the standard error of the difference. The standard error of the difference is calculated by taking the square root of the sum of the variance of the coefficients. Under appropriate normality assumptions, this statistic is a standard normal deviate.

SOURCE: McGee and Gordon (*168*).

laborers had similarly low incidences, but the numbers of cases were too few for more definitive analysis of the influence of occupation (*29*). At all levels of the major risk factors, the incidence of CHD was higher in white than in black men, but some differences were smaller in the higher ranges of the risk factors. The absolute rates for white men were higher than for black men whether they were smokers (including ex-smokers) or nonsmokers, but the relative risk for white male smokers compared with nonsmokers was 2, whereas the relative risk in black male smokers compared with nonsmokers was 3 (*107*).

Multivariate analyses were performed to evaluate differential risk between the black and the white men in Evans County (*146*). A multiple logistic model for the white men was developed using as

explanatory variables smoking, diastolic blood pressure multiplied by age, abnormal electrocardiogram, and cholesterol multiplied by age. This predicted the total incidence and the cases by decile of risk quite well among the white men. When this model was applied to the risk factor levels of the black men ranked by decile of relative risk, four times as many cases were predicted as had been observed (54 predicted, but only 13 actually observed). However, when the multiple logistic model was constrained by an appropriate constant, the number of cases fit the black data satisfactorily. This is consistent with the view that cigarette smoking and the other risk factors are as important in the blacks as in the whites, but that the blacks were protected by some factor that was not accounted for in the analysis (*146*).

The Seven Countries Study

In the Seven Countries study, the risk of CHD in U.S. railroad men resident in the northwest sector of the United States was compared with the risk of CHD in men living in contrasting environments in Europe and Japan. In the Pooling Project, the U.S. railroad men were found to have levels of risk factors comparable to the other principal cohorts, but the total number of cases was 16 percent lower than the number predicted by average parameters of the Pooling Project data.

The relationships of risk factors measured at entry to the subsequent incidence of CHD were less uniform in those cohorts of the Seven Countries study with a low incidence of CHD events, and the absolute incidence at specified levels of the risk factors was significantly different.

With parameters developed from the data of the U.S. railroad cohort and using the risk factors cigarette smoking, systolic blood pressure, serum cholesterol, body mass index, pulse rate, and age, 226 CHD deaths were predicted for the northern European cohorts, whereas 272 CHD deaths were actually observed. Although the predicted number of cases based on the experience of U.S. railroad men underestimated the number observed in the northern European cohorts by 20 percent, there was excellent correlation between predicted and observed cases by decile of risk. Furthermore, the absolute rate in the northern European cohorts was close to that predicted by average U.S. experience as observed in the Pooling Project.

In contrast to the northern European cohorts, the southern European cohorts had substantially fewer CHD deaths than were predicted by the multiple logistic equation based on the experience of the U.S. railroad cohort. As shown in Figure 14, 66 percent more cases were predicted than observed; however, rank order by decile of risk correlated closely ($r = 0.92$). Consistent with these differences,

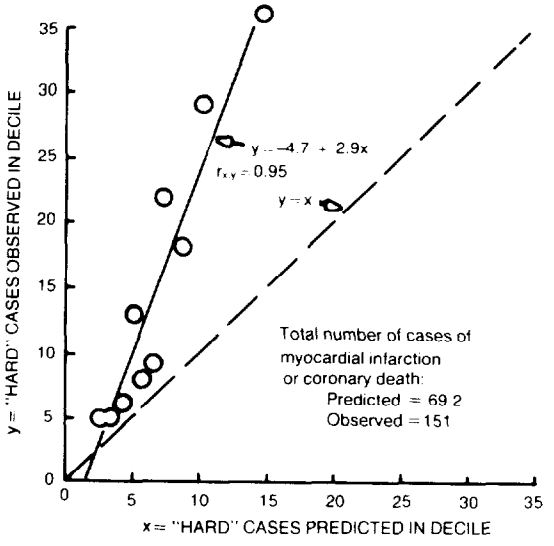


FIGURE 14.—Ten-year incidence of coronary death or myocardial infarction (hard CHD) in northern Europe, in the deciles of probability estimated from the logistic coefficients from the data on the men in southern Europe and the number of such incidence cases actually observed in those deciles

SOURCE: Keys (*143*).

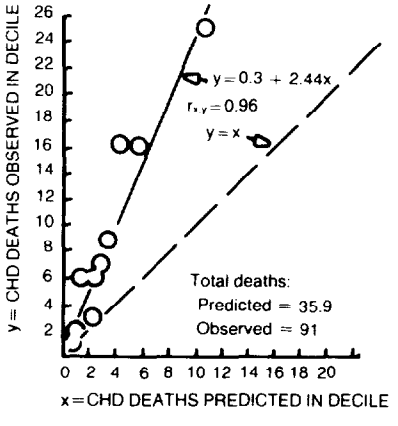


FIGURE 15.—Ten-year deaths from coronary heart disease in northern Europe, predicted in the deciles of probability estimated from the logistic coefficients from the data on the men in southern Europe and the number of coronary deaths actually found in those deciles

SOURCE: Keys (*143*).

multivariate equations for CHD incidence and for CHD deaths based on southern European experience underpredicted CHD incidence and death rates for the cohorts in northern Europe by a factor of 2.5 (Figures 14 and 15). Nevertheless, by rank order of risk, correlation between predicted and observed events was excellent ($r = 0.98$).

These detailed comparisons of the results from major epidemiologic investigations of CHD incidence do indicate that there is excellent agreement in the relationships of cigarette smoking and the other risk factors to the subsequent development of CHD in white men living in the United States and northern Europe. The agreement is close enough so that risk of CHD may be predicted well by the level of the major risk factors, using equations that are largely interchangeable among widely separated cohorts living in these different regions.

References

(1) ALPERT, J.S., BRAUNWALD, E. Pathological and clinical manifestations of acute myocardial infarction. In: Braunwald, E. (Editor). *Heart Disease: A Textbook of Cardiovascular Medicine.* Volume 2. Philadelphia, W. B. Saunders Company, 1980, pp. 1309–1352.

(2) AMERICAN HEART ASSOCIATION. *Heart Facts 1983.* Dallas, American Heart Association, National Center, 1983, 28 pp.

(3) ANDERSON, A.E., Jr., FORAKER, A.G. Smoking, mortality, and sex in a community hospital necropsy population. *Southern Medical Journal* 74(9): 1097–1100, September 1981.

(4) ANDERSON, A.J., LOEFFLER, R.F., BARBORIAK, J.J., RIMM, A.A. Occlusive coronary artery disease and parental history of myocardial infarction. *Preventive Medicine* 8(3): 419–428, May 1979.

(5) ARKWRIGHT, P.D., BEILIN, L.J., ROUSE, I., ARMSTRONG, B.K., VANDONGEN, R. Effects of alcohol use and other aspects of lifestyle on blood pressure levels and prevalence of hypertension in a working population. *Circulation* 66(1): 60–66, July 1982.

(6) ARTHES, F.G., MASI, A.T. Myocardial infarction in younger women. Associated clinical features and relationship to use of oral contraceptive drugs. *Chest* 70(5): 574–583, November 1976.

(7) AUERBACH, O., CARTER, H.W. Smoking and the heart. In: Bristow, M.R. (Editor). *Drug-Induced Heart Disease. Meyler and Peck's Drug-Induced Diseases.* Volume 5. Amsterdam, Elsevier/North Holland Biomedical Press, 1980, pp. 359–376.

(8) AUERBACH, O., CARTER, H.W., GARFINKEL, L., HAMMOND, E.C. Cigarette smoking and coronary artery disease. A macroscopic and microscopic study. *Chest* 70(6): 697–705, December 1976.

(9) AUERBACH, O., HAMMOND, E.C., GARFINKEL, L. Smoking in relation to atherosclerosis of the coronary arteries. *New England Journal of Medicine* 273(15): 775–779, October 7, 1965.

(10) BABA, N., BASHE, W.J., Jr., KELLER, M.D., GEER, J.C., ANTHONY, J.R. Pathology of atherosclerotic heart disease in sudden death. I. Organizing thrombosis and acute coronary vessel lesions. *Circulation* 51 and 52 (Supplement III): III-53—III-59, December 1975.

(11) BARBORIAK, J.J., ANDERSON, A.J., HOFFMANN, R.G. Smoking, alcohol and coronary artery occlusion. *Atherosclerosis* 43(2/3): 277–282, June 1982.

(12) BASHE, W.J., Jr., BABA, N., KELLER, M.D., GEER, J.C., ANTHONY, J.R. Pathology of atherosclerotic heart disease in sudden death. II. The significance of myocardial infarction. *Circulation* 51 and 52 (Supplement III): III-63—III-77, December 1975.

(13) BEAGLEHOLE, R., TROST, D.C., TAMIR, I., KWITEROVICH, P., GLUECK, C.J., INSULL, W., CHRISTENSEN, B. Plasma high-density lipoprotein cholesterol in children and young adults. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-83—IV-92, November 1980.

(14) BELSKY, J.L., KAGAN, A., SYME, S.L. *Epidemiologic Studies of Coronary Heart Disease and Stroke in Japanese Men Living in Japan, Hawaii and California. Research Plan.* Atomic Bomb Casualty Commission Technical Report 12–71, 1971. Microfiched and stored at Bay Microfilm, Inc., 737 Loma Verde Avenue, Palo Alto, California.

(15) BENGTSSON, C., LINDQUIST, O. Coronary heart disease during the menopause. In: Oliver, M.F. (Editor). *Coronary Heart Disease in Young Women.* Edinburgh, Churchill Livingstone, 1978, pp. 234-242.

(16) BENGTSSON, C., RYBO, G., WESTERBERG, H. Number of pregnancies, use of oral contraceptives and menopausal age in women with ischemic heart disease, compared to a population sample of women. *Acta Medica Scandinavica* (Supplement 549): 75–81, October 30, 1973.

(17) BEST, E.W.R. *A Canadian Study of Smoking and Health.* Ottawa, Department of National Health and Welfare, Epidemiology Division, Health Services Branch, Biostatistics Division, Research and Statistics Directorate, 1966, 137 pp.

(18) BEST, E.W.R., JOSIE, G.H., WALKER, C.B. A Canadian study of mortality in relation to smoking habits. A preliminary report. *Canadian Journal of Public Health* 52(3): 99–106, March 1961.

(19) BLACKBURN, H., CHAPMAN, J., DAWBER, T.R., DOYLE, J.T., EPSTEIN, F.H., KANNEL, W.B., KEYS, A., MOORE, F., PAUL, O., STAMLER, J., TAYLOR, H.L. Revised data for 1970 ICHD report. *American Heart Journal* 94(4): 539–540, October 1977.

(20) BLOXHAM, C.A., BEEVERS, D.G., WALKER, J.M. Malignant hypertension and cigarette smoking. *British Medical Journal* 1(6163): 581–583, 1979.

(21) BODEN, L.I. The economic impact of environmental disease on health care delivery. *Journal of Occupational Medicine* 18(7): 467–472, July 1976.

(22) BÖTTIGER, L.E., CARLSON, L.A. Risk factors for death for males and females. A study of the death pattern in the Stockholm prospective study. *Acta Medica Scandinavica* 211(6): 437–442, 1982.

(23) BRADLEY, D.D., WINGERD, J., PETITTI, D.B., KRAUSS, R.M., RAMCHARAN, S. Serum high-density-lipoprotein cholesterol in women using oral contraceptives, estrogens and progestins. *New England Journal of Medicine* 299(1): 17–20, July 6, 1978.

(24) BRAND, R.J. Coronary-prone behavior as an independent risk factor for coronary heart disease. In: Dembroski, T.M., Weiss, S.M., Shields, J.L., Haynes, S., Feinleib, M. (Editors). *Coronary-Prone Behavior.* New York, Springer-Verlag, 1978, pp. 11–24.

(25) BRAND, R.J., ROSENMAN, R.H., SHOLTZ, R.I., FRIEDMAN, M. Multivariate prediction of coronary heart disease in the Western Collaborative Group study compared to the findings of the Framingham study. *Circulation* 53(2): 348–355, February 1976.

(26) CARLSON, L.A., BOTTIGER, L.E. Ischaemic heart-disease in relation to fasting values of plasma triglycerides and cholesterol. Stockholm prospective study. *Lancet* 1(7756): 865–870, April 22, 1972.

(27) CARLSON, L.A., BOTTIGER, L.E., AHFELDT, P.-E. Risk factors for myocardial infarction in the Stockholm prospective study. A 14-year follow-up focussing on the role of plasma triglycerides and cholesterol. *Acta Medica Scandinavica* 206(5): 351–360, 1979.

(28) CASSEL, J., HEYDEN, S., BARTEL, A.G., KAPLAN, B.H., TYROLER, H.A., CORNONI, J.C., HAMES, C.G. Incidence of coronary heart disease by ethnic group, social class, and sex. *Archives of Internal Medicine* 128(6): 901–906, December 1971.

(29) CASSEL, J., HEYDEN, S., BARTEL, A.G., KAPLAN, B.H., TYROLER, H.A., CORNONI, J.C., HAMES, C.G. Occupation and physical activity and coronary heart disease. *Archives of Internal Medicine* 128(6): 920–928, December 1971.

(30) CASTELLI, W.P., DAWBER, T.R., FEINLEIB, M., GARRISON, R.J., McNAMARA, P.M., KANNEL, W.B. The filter cigarette and coronary heart disease: The Framingham study. *Lancet* 2(8238): 109–113, July 18, 1981.

(31) CEDERLOF, R., FRIBERG, L., HRUBEC Z., LORICH, U. *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity.* A ten-year follow-up in a probability sample of 55,000 Swedish subjects, age 18–69, Part 1 and Part 2. Stockholm, Sweden, Department of Environmental Hygiene, The Karolinska Institute, 1975, 91 pp.

(32) CHESEBRO, J.H., FUSTER, V., ELVEBACK, L.R., FRYE, R.L. Strong family history and cigarette smoking as risk factors of coronary artery disease in young adults. *British Heart Journal* 47(1): 78–83, January 1982.

(33) COBB, L.A., WERNER, J.A., TROBAUGH, G.B. Sudden cardiac death: I. A decade's experience with out-of-hospital resuscitation. *Modern Concepts of Cardiovascular Disease* 49(6): 31–36, June 1980.

(34) COHN, P.F., BRAUNWALD, E. Chronic coronary artery disease. In: Braunwald, E. (Editor). *Heart Disease: A Textbook of Cardiovascular Medicine.* Volume 2. Philadelphia, W.B. Saunders Company, 1980, pp. 1387–1436.

(35) CRIQUI, M.H., WALLACE, R.B., HEISS, G., MISHKEL, M., SCHONFELD, G., JONES, G.T.L. Cigarette smoking and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-70—IV-76, November 1980.

(36) CRIQUI, M.H., WALLACE, R.B., MISHKEL, M., BARRET-CONNOR, E., HEISS, G. Alcohol consumption and blood pressure. The Lipid Research Clinics prevalence study. *Hypertension* 3(5): 557–565, September-October 1981.

(37) CRYER, P.E., HAYMOND, M.W., SANTIAGO, J.V., SHAH, S.O. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *New England Journal of Medicine* 295(11): 573–577, September 9, 1976.

(38) CULLEN, K., STENHOUSE, N.S., WEARNE, K.L. Alcohol and mortality in the Busselton study. *International Journal of Epidemiology* 11(1): 67–70, March 1982.

(39) DALEN, J.E., OCKENE, I.S., ALPERT, J.S. Coronary spasm, coronary thrombosis and myocardial infarction. *Transactions of the American Clinical and Climatological Association* 93: 87–97, 1981.

(40) DAWBER, T.R. *The Framingham Study: The Epidemiology of Atherosclerotic Disease.* Cambridge, Harvard University Press, 1980, 267 pp.

(41) DEDONDER-DECOOPMAN, E., FIEVET-DESREUMAUX, C., CAMPOS, E., MOULIN, S., DEWAILLY, P., SEZILLE, G., JAILLARD, J. Plasma levels of VLDL + LDL-cholesterol, HDL-cholesterol, triglycerides and apolipoproteins B and A-I in a healthy population. *Atherosclerosis* 37(4): 559–568, December 1980.

(42) DIMSDALE, J.E., HUTTER, A.M., Jr., HACKETT, T.P., BLOCK, P.C. Predicting extensive coronary artery disease. *Journal of Chronic Diseases* 34(11): 513–517, 1981.

(43) DOLL, R., GRAY, R., HAFNER, B., PETO, R. Mortality in relation to smoking: 22 years' observations on female British doctors. *British Medical Journal* 280(6219): 967–971, April 5, 1980.

(44) DOLL, R., HILL, A.B. Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 205–268.

(45) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 2(6051): 1525–1536, December 25, 1976.

(46) DORN, H.F. Tobacco consumption and mortality from cancer and other diseases. *Public Health Reports* 74(7): 581–593, July 1959.

(47) DOYLE, J.T. Mechanisms and prevention of sudden death. *Modern Concepts of Cardiovascular Disease* 45(7): 111–116, July 1976.

(48) DOYLE, J.T., DAWBER, T.R., KANNEL, W.B., HESLIN, A.S., KAHN, H.A. Cigarette smoking and coronary heart disease. Combined experience of the Albany and Framingham studies. *New England Journal of Medicine* 266(16): 796–801, April 19, 1962.

(49) DOYLE, J.T., DAWBER, T.R., KANNEL, W.B., KINCH, S.H., KAHN, H.A. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, NY, and Framingham, Mass., studies. *Journal of the American Medical Association* 190(10): 108–112, December 7, 1964.

(50) DOYLE, J.T., KANNEL, W.B., McNAMARA, P.M., QUICKENTON, P., GORDON, T. Factors related to suddeness of death from coronary disease: Combined Albany-Framingham studies. *American Journal of Cardiology* 37(7): 1073–1078, June 1976.

(51) DUCIMETIERE, P., ESCHWEGE, E., RICHARD, J., CLAUDE, J., ELGRISHI, I. Relationship of glucose tolerance to prevalence of ECG abnormalities and to annual mortality from cardiovascular disease: Results of the Paris prospective study. *Journal of Chronic Diseases* 32(11/12): 759–766, 1979.

(52) DYER, A.R., STAMLER, J., SHEKELLE, R.B., SCHOENBERGER, J.A., STAMLER, R., SHEKELLE, S., BERKSON, D.M., PAUL, O., LEPPER, M.H., LINDBERG, H.A. Pulse pressure—I. Level and associated factors in four Chicago epidemologic studies. *Journal of Chronic Diseases* 35(4): 259–273, 1982.

(53) DYER, A.R., STAMLER, J., SHEKELLE, R.B., SCHOENBERGER, J.A., STAMLER, R., SHEKELLE, S., BERKSON, D.M., PAUL, O., LEPPER, M.H., LINDBERG, H.A. Pulse pressure—II. Factors associated with follow-up values in three Chicago epidemiologic studies. *Journal of Chronic Diseases* 35(4): 275–282, 1982.

(54) DYER, A.R., STAMLER, J., UBELL, E., PAUL, O., LEPPER, M.H., BERKSON, D.M., LINDBERG, H.A. A self-scoring five-question risk test for coronary heart disease. *Circulation* 60(4): 914–920, October 1979.

(55) EISENBERG, M.S., BERGNER, L., HEARNE, T. Out-of-hospital cardiac arrest: A review of major studies and a proposed uniform reporting system. *American Journal of Public Health* 70(3): 236–240, March 1980.

(56) EISENBERG, M.S., HALLSTROM, A., BERGNER, L. Long-term survival after out-of-hospital cardiac arrest. *New England Journal of Medicine* 306(22): 1340–1343, June 3, 1982.

(57) ELLIOT, J.M., SIMPSON, F.O. Cigarettes and accelerated hypertension. *New Zealand Medical Journal* 91(662): 447–449, June 25, 1980.

(58) ENGEL, H.J., PAGE, H.L., Jr., CAMPBELL, W.B. Coronary artery disease in young women. *Journal of the American Medical Association* 230(11): 1531–1534, December 16, 1974.

(59) ENGER, S.C., HERBJORNSEN, K., ERIKSSEN, J., FRETLAND, A. High density lipoproteins (HDL) and physical activity: The influence of physical exercise, age and smoking on HDL-cholesterol and the HDL-/total cholesterol ratio. *Scandinavian Journal of Clinical and Laboratory Investigation* 37(3): 251–255, May 1977.

(60) ENGLISH, J.P., WILLIUS, F.A., BERKSON, J. Tobacco and coronary disease. *Journal of the American Medical Association* 115(16): 1327–1329, October 19, 1940.

(61) EPSTEIN, F.H., OSTRANDER, L.D., Jr., JOHNSON, B.C., PAYNE, M.W., HAYNER, N.S., KELLER, J.B., FRANCIS, T., Jr. Epidemiological studies of cardiovascular disease in a total community—Tecumseh, Michigan. *Annals of Internal Medicine* 62(6): 1170–1187, June 1965.

(62) FAGER, G., WIKLUND, O., OLOFSSON, S.-O., WILHELMSSON, C., BONDJERS, G. Serum apolipoprotein levels in relation to acute myocardial infarction and its risk factors. Apolipoprotein A-I levels in male survivors of myocardial infarction. *Atherosclerosis* 36(1): 67–74, May 1980.

(63) FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES. *Preventive Medicine—U.S.A.* A Report of the Task Force on Preventive Medicine. Prodist, N.Y., 1976, 836 pp.

(64) FRASER, G.E., UPSDELL, M. Alcohol and other discriminants between cases of sudden death and myocardial infarction. *American Journal of Epidemiology* 114(4): 462–476, October 1981.

(65) FREESTONE, S., RAMSAY, L.E. Effect of coffee and cigarette smoking on the blood pressure of untreated and diuretic-treated hypertensive patients. *American Journal of Medicine* 73(9): 348–353, September 1982.

(66) FRENCH-BELGIAN COLLABORATIVE GROUP. Ischemic heart disease and psychological patterns. Prevalence and incidence studies in Belgium and France. *Advances in Cardiology* 29: 25–31, 1982.

(67) FRIEDMAN, G.D., DALES, L.G., URY, H.K. Mortality in middle-aged smokers and nonsmokers. *New England Journal of Medicine* 300(5): 213–217, February 1, 1979.

(68) FRIEDMAN, G.D., KLATSKY, A.L., SIEGELAUB, A.B. Predictors of sudden cardiac death. *Circulation* 51 and 52(Supplement III): III-164—III-169, December 1975.

(69) FRIEDMAN, G.D., PETITTI, D.B., BAWOL, R.D., SEIGELAUB, A.B. Mortality in cigarette smokers and quitters. Effect of base-line differences. *New England Journal of Medicine* 304(23): 1407–1410, June 4, 1981.

(70) FRIEDMAN, G.D., SEIGELAUB, A.B. Changes after quitting cigarette smoking. *Circulation* 61(4): 716–723, April 1980.

(71) FRIEDMAN, M. Type A behavior pattern: Some of its pathophysiological components. *Bulletin of the New York Academy of Medicine* 53(7): 593–604, September 1977.

(72) FURBERG, C., ROMO, M., LINKO, E., SILTANEN, P., TIBBLIN, G., WILHELMSEN, L. Sudden coronary death in Scandinavia. A report from Scandinavian coronary heart disease registers. *Acta Medica Scandinavica* 201(6): 553–557, 1977.

(73) GARFINKEL, L. Cardiovascular mortality and cigarette smoking. IN: Ramström, L.M. (Editor). *The Smoking Epidemic, A Matter of Worldwide Concern.* Proceedings of the Fourth World Conference on Smoking and Health, Stockholm, Almqvist and Wilsell International, 1980, pp. 41–44.

(74) GARRISON, R.J., KANNEL, W.B., FEINLEIB, M., CASTELLI, W.P., McNAMARA, P.M., PADGETT, S.J. Cigarette smoking and HDL cholesterol: The Framingham offspring study. *Atherosclerosis* 30(1): 17–25, May 1978.

(75) GILLUM, R.F. Coronary heart disease in black populations. I. Mortality and morbidity. *American Heart Journal* 104(4, part 1): 839–851, October 1982.

(76) GILLUM, R.F., GRANT, C.T. Coronary heart disease in black populations. II. Risk factors. *American Heart Journal* 104(4, part 1): 852–864, October 1982.

(77) GILLUM, R.F., PAFFENBARGER, R.S., Jr. Chronic disease in former college students. XVII. Sociocultural mobility as a precursor of coronary heart disease and hypertension. *American Journal of Epidemiology* 108(4): 289–298, October 1978.

(78) GLOMSET, J.A. High-density lipoproteins in human health and disease. *Advances in Internal Medicine* 25: 91–116, 1980.

(79) GLUECK, C.J., TAYLOR, H.L., JACOBS, D., MORRISON, J.A., BEAGLEHOLE, R., WILLIAMS, O.D. Plasma high-density lipoprotein cholesterol: Association with measurements of body mass. The Lipid Research Clinics program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-62—IV-69, November 1980.

(80) GOLDBOURT, U., MEDALIE, J.H. High density lipoprotein cholesterol and incidence of coronary heart disease—The Israeli ischemic heart disease study. *American Journal of Epidemiology* 109(3): 296–308, March 1979.

(81) GOLDBOURT, U., MEDALIE, J.H., NEUFELD, H.N. Clinical myocardial infarction over a five-year period—III. A multivariate analysis of incidence, the Israel ischemic heart disease study. *Journal of Chronic Diseases* 28(4): 217–237, April 1975.

(82) GOLDSTEIN, J.L., BROWN, M.S. Lipoprotein receptors: Genetic defense against atherosclerosis. *Clinical Research* 30(5): 417–426, December 1982.

(83) GORDON, T. Further mortality experience among Japanese Americans. *Public Health Reports* 82(11): 973–984, November 1967.

(84) GORDON, T., CASTELLI, W.P., HJORTLAND, M.C., KANNEL, W.B., DAWBER, T.R. High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. *American Journal of Medicine* 62: 707–714, May 1977.

(85) GORDON, T., GARCIA-PALMIERI, M.R., KAGAN, A., KANNEL, W.B., SCHIFFMAN, J. Differences in coronary heart disease in Framingham, Honolulu and Puerto Rico. *Journal of Chronic Diseases* 27(7/8): 329–344, September 1974.

(86) GORDON, T., KANNEL, W.B. The Framingham, Massachusetts, study twenty years later. In: Kessler, I.I., Levin, M.L. (Editors). *The Community as an Epidemiologic Laboratory: A Casebook of Community Studies.* Baltimore, The Johns Hopkins University Press, 1970, pp. 123–146.

(87) GORLIN, R. Role of coronary vasospasm in the pathogenesis of myocardial ischemia and angina pectoris. *American Heart Journal* 103(4, part 2): 598–603, April 1982.

(88) GREIG, M., PEMBERTON, J., HAY, I., MacKENZIE, G. A prospective study of the development of coronary heart disease in a group of 1202 middle-aged men. *Journal of Epidemiology and Community Health* 34(1): 23–30, March 1980.

(89) GRUNDY, P.F. *Mortality in Relation to Lung Function, Respiratory Symptoms, Obesity and Smoking Habit.* Volume I. Heath Park, Cardiff, Welsh National School of Medicine, April 1979, 124 pp.

(90) GSELL, O., ABELIN, T., WIELTCHNIG, E. Rauchen und Mortalitat der Schweizer Arzte: Resultata nach 18 Jahriger Beobachtung. [Smoking and mortality of Swiss physicians: Results after 18 years of observation.] *Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften* 35(1–3): 71–82, March 1979.

(91) GYNTELBERG, F., LAURIDSEN, L., PEDERSEN, P.B., SCHUBELL, K. Smoking and risk of myocardial infarction in Copenhagen men aged 40–59 with special reference to cheroot smoking. *Lancet* 1(8227): 987–989, May 2, 1981.

(92) HAMMAN, R.F., BARANCIK, J.I., LILIENFELD, A.M. Patterns of mortality in the Old Order Amish. I. Background and major causes of death. *American Journal of Epidemiology* 114(6): 845–861, December 1981.

(93) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 127–204.

(94) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167–182, August 1969.

(95) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., KEW, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. *Environmental Research* 12(3): 263–274, December 1976.

(96) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men: II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294–1308, March 15, 1958.

(97) HANSEN, J.F. Chest pain, risk factors and coronary artery disease. *Danish Medical Bulletin* 27(3): 148–152, July 1980.

(98) HASIN, Y., EISENBERG, S., FRIEDLANDER, J., LEWIS, B.S., GOTSMAN, M.S. Relationship between extent of coronary artery disease and correlative risk factors. *American Heart Journal* 98(5): 555–561, November 1979.

(99) HASKELL, W.L., TAYLOR, H.L., WOOD, P.D., SCHROTT, H., HEISS, G. Strenuous physical activity, treadmill exercise test performance and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-53—IV-61, November 1980.

(100) HAVEL, R.J., GOLDSTEIN, J.L., BROWN, M.S. Lipoproteins and lipid transport. In: Bondy, P.K., Rosenberg, L.E. (Editors). *Metabolic Control and Disease.* Eighth Edition. Philadelphia, W.B. Saunders Company, 1980, pp. 393–494.

(101) HAVLIK, R.J., FEINLEIB, M., THOM, T., KRAMES, B., SHARRETTA, A.R., GARRISON, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* Bethesda, Maryland, October 24–25, 1978. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health. NIH Publication No. 79–1610, May 1979, 399 pp.

(102) HAVLIK, R.J., GARRISON, R.J., FEINLEIB, M., PADGETT, S., CASTELLI, W.P., McNAMARA, P.M. Evidence for additional blood pressure correlates in adults 20–56 years old. *Circulation* 61(4): 710–715, April 1980.

(103) HAYNES, S.G., FEINLEIB, M. Women, work and coronary heart disease: Prospective findings from the Framingham heart study. *American Journal of Public Health* 70(2): 133–141, February 1980.

(104) HAYNES, S.G., FEINLEIB, M., KANNEL, W.B. The relationship of psychosocial factors to coronary heart disease in the Framingham study. III. Eight-year incidence of coronary heart disease. *American Journal of Epidemiology* 111(1): 37–58, 1980.

(105) HEISS, G., HASKELL, W., MOWERY, R., CRIQUI, M.H., BROCKWAY, M., TYROLER, H.A. Plasma high-density lipoprotein cholesterol and socioeconomic status. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-108–IV-115, November 1980.

(106) HEISS, G., TAMIR, I., DAVIS, C.E., TYROLER, H.A., RIFKIND, B.M., SCHONFELD, G., JACOBS, D., FRANTZ, I.D., Jr. Lipoprotein-cholesterol distributions in selected North American populations: The Lipid Research Clinics Program prevalence study. *Circulation* 61(2): 302–315, February 1980.

(107) HEYDEN, S., CASSEL, J.C., BARTEL, A., TYROLER, H.A., HAMES, C.G., CORNONI, J.C. Body weight and cigarette smoking as risk factors. *Archives of Internal Medicine* 128(6): 915–919, December 1971.

(108) HIGGENBOTTAM, T., SHIPLEY, M.J., ROSE, G. Cigarettes, lung cancer, and coronary heart disease: The effects of inhalation and tar yield. *Journal of Epidemiology and Community Health* 36(2): 113–117, June 1982.

(109) HINKLE, L.E., Jr. The immediate antecedents of sudden death. *Acta Medica Scandinavica* (Supplement)651: 207–217, 1981.

(110) HINKLE, L.E., Jr. Short-term risk factors for sudden death. *Annals of the New York Academy of Sciences* 382: 22–38, 1982.

(111) HIRAYAMA, T. Kitsuen to junkanki shikkan no kankei ni kansuru ekigakuteki kenkyu. [Smoking and cardiovascular disease—An epidemiological study.] *Korei Igaku* 13(3): 86–91, 1975.

(112) HIRAYAMA, T. Kitsuen to kyoketsusei shinzobyo to no kankei ni kansuru ekigakuteki kenkyu. [An epidemiological study on smoking and ischemic heart disease.] *General Clinical Journal* 27(2): 265–274, 1978.

(113) HIRAYAMA, T. Kitsuen to domyaku koka to no kankei ni kansuru ekigakuteki kenkyu. [Smoking and arteriosclerosis—An epidemiological study.] *Chiryo* 61(4): 25–32, 1979.

(114) HIRAYAMA, T. Kitsuen to domyaku koka to no kankei ni kansuru ekigakuteki kenkyu. [Smoking and arteriosclerosis—An epidemiological study.] *Saishin Igaku* 36(4): 798–809, 1981.

(115) HIRAYAMA, T. Kitsuen to inshu to seijinbyo to no kankei ni kansuru ekigakuteki kenkyu. [An epidemiological study on smoking and drinking and chronic diseases.] *Special Issue—Alcohol, Tobacco and Adult Diseases* 12(2): 11–19, 1981.

(116) HIRAYAMA, T., HAMANO, Y. Kitsuen to shuyo shiin betsu shibo ritsu to no kankei. [Smoking and mortality from major causes of death.] *Eisei No Shibyo* 28(4): 3–18, 1981.

(117) HOLME, I., HELGELAND, A., HJERMANN, I., LEREN, P., LUND-LARSEN, P.G. Four and two-thirds years incidence of coronary heart disease in middle-aged men: The Oslo study. *American Journal of Epidemiology* 112(1): 149–160, July 1980.

(118) HOLMES, D.R., Jr., ELVEBACK, L.R., FRYE, R.L., KOTTKE, B.A., ELLEFSON, R.D. Association of risk factor variables and coronary artery disease documented with angiography. *Circulation* 63(2): 293–299, February 1981.

(119) HOPKINS, P.N., WILLIAMS, R.R. A survey of 246 suggested coronary risk factors. *Atherosclerosis* 40(1): 1–52, August/September 1981.

(120) HRUBEC, Z., ZUKEL, W.J. Epidemiology of coronary heart disease among young army males of World War II. *American Heart Journal* 87(6): 722–730, June 1974.

(121) HUBERT, H.B., HOLFORD, T.R., KANNEL, W.B. Clinical characteristics and cigarette smoking in relation to prognosis of angina pectoris in Framingham. *American Journal of Epidemiology* 115(2): 231–242, February 1982.

(122) HULLEY, S., ASHMAN, P., KULLER, L., LASSER, N., SHERWIN, R. HDL-cholesterol levels in the Multiple Risk Factor Intervention Trial (MRFIT) by the MRFIT Research Group. *Lipids* 14(1): 119–125, January 1979.

(123) HULLEY, S.B., COHEN, R., WIDDOWSON, G. Plasma high-density lipoprotein cholesterol level: Influence of risk factor intervention. *Journal of the American Medical Association* 238(21): 2269–2271, November 21, 1977.

(124) INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES. Primary prevention of the atherosclerotic diseases. *Circulation* 42(6): A-55—A-95, December 1970.

(*125*) ISLES, C., BROWN, J.J., CUMMING, A.M.M., LEVER, A.F., McAREAVEY, D., ROBERTSON, J.I.S., HAWTHORNE, V.M., STEWART, G.M., ROBERTSON, J.W.K., WAPSHAW, J. Excess smoking in malignant-phase hypertension. *British Medical Journal* 1(6163): 579–581, March 3, 1979.

(*126*) ITALIAN RESEARCH GROUP OF THE SEVEN COUNTRIES STUDY. Incidence and prediction of coronary heart disease in two Italian rural population samples followed-up for 20 years. *Acta Cardiologica* 37(2): 129–145, 1982.

(*127*) JAIN, A.K. Cigarette smoking, use of oral contraceptives, and myocardial infarction. *American Journal of Obstetrics and Gynecology* 126(3): 301–307, October 1, 1976.

(*128*) JICK, H., DINAN, B., ROTHMAN, K.J. Oral contraceptives and nonfatal myocardial infarction. *Journal of the American Medical Association* 239(14): 1403–1406, April 3, 1978.

(*129*) JICK, H., PORTER, J., MORRISON, A.S. Relation between smoking and age of natural menopause. Report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *Lancet* 1(8026): 1354–1355, June 25, 1977.

(*130*) KAGAN, A., GORDON, T., RHOADS, G.G., SCHIFFMAN, J.C. Some factors related to coronary heart disease incidence in Honolulu Japanese men: The Honolulu heart study. *International Journal of Epidemiology* 4(4): 271–279, December 1975.

(*131*) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 1–125.

(*132*) KANNEL, W.B. *Habits and Coronary Heart Disease. The Framingham Heart Study.* U.S. Department of Health and Human Services, Public Health Service, National Heart Institute, Heart Information Center, Public Health Service Publication No. 1515, 1966.

(*133*) KANNEL, W.B. Some lessons in cardiovascular epidemiology from Framingham. *American Journal of Cardiology* 37(2): 269–282, February 1976.

(*134*) KANNEL, W.B. Update on the role of cigarette smoking in coronary artery disease. *American Heart Journal* 101(3): 319–328, March 1981.

(*135*) KANNEL, W.B., CASTELLI, W.P., McNAMARA, P.M. Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis. The Framingham study. In: Wynder, E.L., Hoffmann, D. (Editors). *Toward A Less Harmful Cigarette.* A workshop held at the World Conference on Smoking and Health, September 11–13, 1967. National Cancer Institute Monograph 28, U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, June 1968, pp. 9–20.

(*136*) KANNEL, W.B., CASTELLI, W.P., McNAMARA, P.M. Epidemiology of acute myocardial infarction. The Framingham study. *Medicine Today* 2: 56–71, August/September 1968.

(*137*) KANNEL, W.B., DOYLE, J.T., McNAMARA, P.M., QUICKENTON, P., GORDON, T. Precursors of sudden coronary death: Factors related to the incidence of sudden death. *Circulation* 51(4): 606–613, April 1975.

(*138*) KANNEL, W.B., McGEE, D.L., GORDON, T. A general cardiovascular risk profile: The Framingham study. *American Journal of Cardiology* 38(1): 46–51, July 1976.

(*139*) KANNEL, W.B., THOMAS, H.E., Jr. Sudden coronary death: The Framingham study. *Annals of the New York Academy of Sciences* 382: 3–21, 1982.

(*140*) KAUFMAN, D.W., HELMRICH, S.P., ROSENBERG, L., MIETTINEN, O.S., SHAPIRO, S. Nicotine and carbon monoxide content of cigarette smoke and the risk of myocardial infarction in young men. *New England Journal of Medicine* 308(8): 409–413, February 24, 1983.

(*141*) KAVANAGH, T., SHEPHARD, R.J., CHISHOLM, A.W., QURESHI, S., KENNEDY, J. Prognostic indexes for patients with ischemic heart disease enrolled in an exercise-centered rehabilitation program. *American Journal of Cardiology* 44(7): 1230–1240, December 1979.

(*142*) KEIL, J.E., TYROLER, H.A., SANDIFER, S.H., BOYLE, E., Jr. Hypertension: Effects of social class and racial admixture. The results of a cohort study in the black population of Charleston, South Carolina. *American Journal of Public Health* 67(7): 634–639, July 1977.

(*143*) KEYS, A. Smoking habits. In: Keys, A. (Editor). *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease.* Cambridge, Harvard University Press, 1980, pp. 136–160.

(*144*) KEYS, A., TAYLOR, H.L., BLACKBURN, H., BROZEK, H., ANDERSON, J.T., SIMONSON, E. Coronary heart disease among Minnesota business and professional men followed fifteen years. *Circulation* 28(3): 381–395, September 1963.

(*145*) KILLIP, T. Time, place, event of sudden death. *Circulation* 51 and 52(Supplement III): III-160—III-163, December 1975.

(*146*) KLEINBAUM, D.G., KUPPER, L.L., CASSEL, J.C., TYROLER, H.A. Multivariate analysis of risk of coronary heart disease in Evans County, Georgia. *Archives of Internal Medicine* 128: 943–948, December 1971.

(*147*) KLEINBAUM, D.G., KUPPER, L.L., MORGENSTERN, H. *Epidemologic Research. Principles and Quantitative Methods.* Belmont, California, Lifetime Learning Publications, 1982, 529 pp.

(*148*) KOZAREVIC, D., DEMIROVIC, J., GORDON, T., KAELBER, C.T., McGEE, D., ZUKEL, W.J. Drinking habits and coronary heart disease: The Yugoslavia cardiovascular disease study. *American Journal of Epidemiology* 116(5): 748–758, October 1982.

(*149*) KOZAREVIC, D., VOJVODIC, N., GORDON, T., KAELBER, C.T., McGEE, D., ZUKEL, W.J. Drinking habits and death. The Yugoslavia cardiovascular disease study. *International Journal of Epidemiology* 12(2): 145–150, June 1983.

(*150*) KRUEGER, D.E., ELLENBERG, S.S., BLOOM, S., CALKINS, B.M., JACYNA, R., NOLAN, D.C., PHILLIPS, R., RIOS, J.C., SOBIESKI, R., SHEKELLE, R.B., SPECTOR, K.M., STADEL, B.V., STOLLEY, P.D., TERRIS, M. Risk factors for fatal heart attack in young women. *American Journal of Epidemiology* 113(4): 357–370, April 1981.

(*151*) KRUEGER, D.E., ELLENBERG, S.S., BLOOM, S., CALKINS, B.M., MALIZA, C., NOLAN, D.C., PHILLIPS, R., RIOS, J.C., ROSIN, I., SHEKELLE, R.B., SPECTOR, K.M., STADEL, B.V., STOLLEY, P.D., TERRIS, M. Fatal myocardial infarction and the role of oral contraceptives. *American Journal of Epidemiology* 111(6): 655–674, June 1980.

(*152*) KULLER, L. Sudden death in arteriosclerotic heart disease. The case for preventive medicine. *American Journal of Cardiology* 24(5): 617–628, November 1969.

(*153*) KULLER, L., COOPER, M., PERPER, J. Epidemiology of sudden death. *Archives of Internal Medicine* 129(5): 714–719, May 1972.

(*154*) KULLER, L., LILIENFELD, A., FISHER, R. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. *Circulation* 34(6): 1056–1068, December 1966.

(155) KULLER, L., MEILAHN, E., TOWNSEND, M., WEINBERG, G. Control of cigarette smoking from a medical perspective. *Annual Review of Public Health* 3: 153–178, 1982.

(156) KULLER, L., PERPER, J., COOPER, M. Demographic characteristics and trends in arteriosclerotic heart disease mortality: Sudden death and myocardial infarction. *Circulation* 51 and 52(Supplement III): III-1—III-15, December 1975.

(157) LAKE, J.L., HELPERN, M. Sudden unexpected death from natural causes in young adults. A review of 275 consecutive autopsied cases. *Archives of Pathology* 85(1): 10–17, January 1968.

(158) LaPORTE, R.E., CRESANTA, J.L., KULLER, L.H. The relationship of alcohol consumption to atherosclerotic heart disease. *Preventive Medicine* 9(1): 22–40, January 1980.

(159) LEVY, R.I., FEINLEIB, M. Risk factors for coronary artery disease and their management. In: Braunwald, E. (Editor). *Heart Disease: A Textbook of Cardiovascular Medicine.* Volume 2. Philadelphia, W.B. Saunders Company, 1980, pp. 1246–1278.

(160) LIE, J.T., TITUS, J.L. Pathology of the myocardium and the conduction system in sudden coronary death. *Circulation* 51 and 52(Supplement III): III-41—III-52, December 1975.

(161) LIU, K., CEDRES, L.B., STAMLER, J., DYER, A., STAMLER, R., NANAS, S., BERKSON, D.M., PAUL, O., LEPPER, M., LINDBERG, H.A., MARQUARDT, J., STEVENS, E., SCHOENBERGER, J.A., SHEKELLE, R.B., COLLETTE, P., SHEKELLE, S., GARSIDE, D. Relationship of education to major risk factors and death from coronary heart disease, cardiovascular diseases and all causes. Findings of three Chicago epidemiologic studies. *Circulation* 66(6): 1308–1314, December 1982.

(162) LOWN, B. Cardiovascular collapse and sudden cardiac death. In: Braunwald, E. (Editor). *Heart Disease: A Textbook of Cardiovascular Medicine.* Volume 1. Philadelphia, W.B. Saunders Company, 1980, pp. 778–817.

(163) LUCE, B.R., SCHWEITZER, S.O. The economic costs of smoking-induced illness. In: National Institute on Drug Abuse. *Research on Smoking Behavior.* NIDA Research Monograph Series 17, 1977, pp. 221–229.

(164) LUCE, B.R., SCHWEITZER, S.O. Smoking and alcohol abuse: A commparison of their economic consequences. *New England Journal of Medicine* 298(10): 569–571, March 9, 1978.

(165) LYON, J.L., WETZLER, H.P., GARDNER, J.W., KLAUBER, M.R., WILLIAMS, R.R. Cardiovascular mortality in Mormons and non-Mormons in Utah, 1969–1971. *American Journal of Epidemiology* 108(5): 357–366, November 1978.

(166) McCULLY, K.S. Homocystine, atherosclerosis and thrombosis: Implications for oral contraceptive users. *American Journal of Clinical Nutrition* 28(5): 542–549, May 1975.

(167) McEVOY, L., LAND, G. Life-style and death patterns of the Missouri RLDS church members. *American Journal of Public Health* 71(12): 1350–1357, December 1981.

(168) McGEE, D., GORDON, T. The results of the Framingham study applied to four other U.S.-based epidemiologic studies of cardiovascular disease. Section 31. In: Kannel, W.B., Gordon, T. (Editors). *The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Heart and Lung Institute, DHEW Publication No. (NIH) 76–1083, April 1976.

(*169*) MANN, J.I. Oral contraceptives and the cardiovascular risk. In: Oliver, M.F. (Editor) *Coronary Heart Disease in Young Women.* Edinburgh, Churchill Livingstone, 1978, pp. 184–196.

(*170*) MANN, J.I., VESSEY, M.P., THOROGOOD, M., DOLL, R. Myocardial infarction in young women with special reference to oral contraceptive practice. *British Medical Journal* 2(5965): 241–245, May 3, 1975.

(*171*) MANTHEY, J., STOEPPLER, M., MORGENSTERN, W., NÜSSEL, E., OPHERK, D., WEINTRAUT, A., WESCH, H., KÜBLER, W. Magnesium and trace metals: Risk factors for coronary heart disease. Associations between blood levels and angiographic findings. *Circulation* 64(4): 722–729, October 1981.

(*172*) MARGOLIS, J.R., KANNEL, W.B., FEINLEIB, M., DAWBER, T.R., McNAMARA, P.M. Clinical features of unrecognized myocardial infarction—Silent and symptomatic. Eighteen year follow-up: The Framingham study. *American Journal of Cardiology* 32(1): 1–7, July 1973.

(*173*) MARMOT, M.G., ROSE, G., SHIPLEY, M.J., THOMAS, B.J. Alcohol and mortality: A U-shaped curve. *Lancet* 1(8220): 580–583, March 14, 1981.

(*174*) MASERI, A. The changing face of angina pectoris: Practical implications. *Lancet* 1(8327): 746–749, April 2, 1983.

(*175*) MASERI, A., SEVERI, S., De NES, M., L'ABBATE, A., CHIERCHIA, S., MARZILLI, M., BALLESTRA, A.M., PARODI, O., BIAGINI, A., DISTANTE, A. 'Variant' angina: One aspect of the continuous spectrum of vasospastic myocardial ischemia. *American Journal of Cardiology* 42(6): 1019–1035, December 1978.

(*176*) MEDALIE, J.H., KAHN, H.A., NEUFELD, H.N., RISS, E., GOLDBOURT, U. Five-year myocardial infarction incidence—II. Association of single variables to age and birthplace. *Journal of Chronic Diseases* 26(6): 329–349, June 1973.

(*177*) MEDALIE, J.H., KAHN, H.A., NEUFELD, H.N., RISS, E., GOLDBOURT, U., PERLSTEIN, T., ORON, D. Myocardial infarction over a five-year period—I. Prevalence, incidence and mortality experience. *Journal of Chronic Diseases* 26(2): 63–84, February 1973.

(*178*) MICHIGAN HEART ASSOCIATION. *RISKO.* Southfield, Michigan Heart Association, 1967.

(*179*) MIETTINEN, O.S. Proportion of disease caused or prevented by a given exposure, trait or intervention. *American Journal of Epidemiology* 99(5): 323–332, May 1974.

(*180*) MILLER, N.E. The evidence for the antiatherogenicity of high density lipoprotein in man. *Lipids* 13(12): 914–919, December 1978.

(*181*) MORDKOFF, A.M., PARSONS, O.A. The coronary personality: A critique. *Psychosomatic Medicine* 29(1): 1–14, January-February 1977.

(*182*) MORIYAMA, I.M., DAWBER, T.R., KANNEL, W.B. Evaluation of diagnostic information supporting medical certification of deaths from cardiovascular disease. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 405–419.

(*183*) MORIYAMA, I.M., KRUEGER, D.E., STAMLER, J. Accuracy and comparability of mortality statistics. *Cardiovascular Diseases in the United States.* Cambridge, Harvard University Press, 1971, pp. 22–48.

(*184*) MORIYAMA, I.M., KRUEGER, D.E., STAMLER, J. Coronary heart disease. *Cardiovascular Diseases in the United States.* Cambridge, Harvard University Press, 1971, pp. 49–118.

(*185*) MORRIS, J.N., KAGAN, A., PATTISON, D.C., GARDNER, M.J., RAFFLE, P.A.B. Incidence and prediction of ischemic heart disease in London busmen. *Lancet* 2(7463): 553–559, September 10, 1966.

(*186*) MORRIS, J.N., MARR, J.W., CLAYTON, D.G. Diet and heart: A postscript. *British Medical Journal* 2(6098): 1307–1314, November 19, 1977.

(*187*) MUSTARD, J.F., PACKHAM, M.A. Thrombosis and the development of atherosclerosis. Paper presented at the meeting of the American Association of Pathologists and Bacteriologists, Montreal, Canada, 1971. In: Wissler, R.W., Geer, J.C. (Editors). *The Pathogenesis of Atherosclerosis.* Baltimore, The Williams & Wilkins Company, 1972, pp. 214–226.

(*188*) MYRHED, M., FLODERUS, B. Alcohol consumption in relation to factors associated with ischemic heart disease. A Cotwin control study. *Acta Geneticae Medicae et Gemellologiae* 25: 129–132, 1976.

(*189*) NATIONAL INSTITUTES OF HEALTH. *Smoking and Health: A Program to Reduce the Risk of Disease in Smokers.* Status report. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, National Heart, Lung, and Blood Institute, December 1977, 128 pp.

(*190*) NATIONAL CENTER FOR HEALTH STATISTICS. Blood pressure of adults by age and sex, United States, 1960–1962. Blood pressure measurements and distributions and mean levels by age and sex. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 4, June 1964, 40 pp.

(*191*) NATIONAL CENTER FOR HEALTH STATISTICS. Blood pressure of adults by race and area, United States, 1960–1962. Mean blood pressure by race and area. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 5, July 1964, 20 pp.

(*192*) NATIONAL CENTER FOR HEALTH STATISTICS. Heart disease in adults, United States, 1960–1962. A description of the examination and diagnostic procedures with major findings by age, sex, and race. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 6, September 1964, 43 pp.

(*193*) NATIONAL CENTER FOR HEALTH STATISTICS. Weight, height, and selected body dimensions of adults, United States, 1960–1962. Age and sex distributions for weight, height, erect sitting height, normal sitting height, knee height, popliteal height, elbow rest height, thigh clearance height, buttock-knee length, buttock-popliteal length, elbow-to-elbow breadth, and seat breadth. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 8, June 1965, 44 pp.

(*194*) NATIONAL CENTER FOR HEALTH STATISTICS. Hypertension and hypertensive heart disease in adults, United States, 1960–1962. A discussion of the criteria used for the diagnosis of hypertension and hypertensive heart disease, with data on the prevalence of hypertension and hypertensive heart disease by age, sex, and race, and an analysis of differentials by place, family income, education, marital status, usual activity, occupation, and industry. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 13, May 1966, 62 pp.

(*195*) NATIONAL CENTER FOR HEALTH STATISTICS. Serum cholesterol levels of adults, United States, 1960–1962. Serum cholesterol levels by age, sex, race, region, and income. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 22, March 1967, 23 pp.

(*196*) NATIONAL CENTER FOR HEALTH STATISTICS. Blood pressure as it relates to physique, blood glucose, and serum cholesterol, United States, 1960–1962. A tabular presentation of the data and a multiple regression analysis of blood pressure on five somatic measurements and their derivatives, and on blood glucose and serum cholesterol by age, sex, and race. Data from the National Health Survey. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Center for Health Statistics, Division of Health Examination Statistics, Public Health Service Publication No. 1000, Series 11, Number 34, October 1969, 29 pp.

(*197*) NATIONAL CENTER FOR HEALTH STATISTICS. *Monthly Vital Statistics Report. Advance Report, Final Mortality Statistics, 1977.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of Health Research, Statistics, and Technology, National Center for Health Statistics, DHEW Publication No. (PHS)79–1120, Volume 28, No. 1, Supplement, May 11, 1979, 35 pp.

(*198*) NATIONAL CENTER FOR HEALTH STATISTICS. Utilization of short-stay hospitals: Annual summary for the United States, 1980. *Vital and Health Statistics.* U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, National Center for Health Statistics, DHHS Publication No. (PHS)82–1725, Series 13, No. 64, March 1982, 62 pp.

(*199*) NATVIG, H., BORCHGREVINK, C.F., DEDICHEN, J., OWREN, P.A., SCHIOTZ, E.H., WESTLUND, K. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965–66. *Scandinavian Journal of Clinical and Laboratory Investigation* 22(Supplement 105): 1–20, 1968.

(*200*) NEWMAN, W.P., III, TRACY, R.E., STRONG, J.P., JOHNSON, W.D., OALMANN, M.C. Pathology of sudden coronary death. *Annals of the New York Academy of Sciences* 382: 39–49, 1982.

(*201*) NITTER-HAUGE, S., ERIKSSEN, J., THAULOW, E., VATNE, K. Angiographic and risk factor characteristics of subjects with early onset ischaemic heart disease. *British Heart Journal* 46(3): 325–330, September 1981.

(*202*) OLIVA, P.B. Coronary arterial spasm and vasomotion (Part 2). Current concepts regarding their role in ischemic heart disease. *Chest* 82(1): 105–110, July 1982.

(203) OLIVER, M.F. Clinical characteristics and prognosis of angina and myocardial infarction in young women. In: Oliver, M.F. (Editor). *Coronary Heart Disease in Young Women.* Edinburgh, Churchill Livingstone, 1978, pp. 221–233.

(204) ORY, H.W. Association between oral contraceptives and myocardial infarction. A review. *Journal of the American Medical Association* 237(24): 2619–2622, June 13, 1977.

(205) PAFFENBARGER, R.F., Jr., BRAND, R.J., SHOLTZ, R.I., JUNG, D.L. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. *American Journal of Epidemiology* 108(1): 12–18, July 1978.

(206) PAUL, O., LEPPER, M.H., PHELAN, W.H., DUPERTUIS, G.W., MacMILLAN, A., McKEAN, H., PARK, H. A longitudinal study of coronary heart disease. *Circulation* 28(1): 20–31, July 1963.

(207) PELKONEN, R., NIKKILA, E.A., KOSKINEN, S., PENTTINEN, K., SARNA, S. Association of serum lipids and obesity with cardiovascular mortality. *British Medical Journal* 2(6096): 1185–1187, November 5, 1977.

(208) PERPER, J.A., KULLER, L.H., COOPER, M. Arteriosclerosis of coronary arteries in sudden, unexpected deaths. *Circulation* 51 and 52(Supplement III): III-27—III-33, December 1975.

(209) PETERSSON, B., KRANTZ, P., KRISTENSSON, H., TRELL, E., STERNBY, N.H. Alcohol-related death: A major contributor to mortality in urban middle-aged men. *Lancet* 2(8307): 1088–1090, November 13, 1982.

(210) PETITTI, D.B., WINGERD, J., PELLEGRIN, F., RAMCHARAN, S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *Journal of the American Medical Association* 242(11): 1150–1154, September 14, 1979.

(211) PETO, J. The health effects of smoking in women. In: Ramstrom, I.M. (Editor). *The Smoking Epidemic, a Matter of Worldwide Concern.* Stockholm, Almqvist and Wiksell International, 1979, pp. 45–50.

(212) PHILLIPS, N.R., HAVEL, R.J., KANE, J.P. Levels and interrelationships of serum and lipoprotein cholesterol and triglycerides. Association with adiposity and the consumption of ethanol, tobacco, and beverages containing caffeine. *Arteriosclerosis* 1(1): 13–24, January/February 1981.

(213) PHILLIPS, N.R., HAVEL, R.J., KANE, J.P. Serum apolipoprotein A-I levels. Relationship to lipoprotein lipid levels and selected demographic variables. *American Journal of Epidemiology* 116(2): 302–313, August 1982.

(214) POOLING PROJECT RESEARCH GROUP. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. *Journal of Chronic Diseases* 31(4): 201–306, April 1978.

(215) RABKIN, S.W., BOYKO, E., STREJA, D.A. Relationship of weight loss and cigarette smoking to changes in high-density lipoprotein cholesterol. *American Journal of Clinical Nutrition* 34(9): 1764–1768, September 1981.

(216) REGAN, T.J. Alcohol: Is it a risk for cardiovascular disease? *Cardiology Series* 5(4): 6–27, 1982.

(217) RHOADS, G.G., GULBRANDSEN, C.L., KAGAN, A. Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. *New England Journal of Medicine* 294(6): 293–298, February 5, 1976.

(218) RICHARD, J.L., DUCIMETIERE, P., BONNAUD, G., CLAUDE, J.R., LELLOUCH, J., SCHWARTZ, D., DiMATTEO, J. Incidence et evaluation du risque de maladie coronarienne: L'etude prospective parisienne. [Incidence and evaluation of risk of coronary heart disease: The Parisian prospective study]. *Archives des Maladies du Coeur et des Vaisseaux* 70(5): 531–540, May 1977.

(219) RICHTER, B.J., GORI, G.B. Demographic and economic effects of the prevention of early mortality associated with tobacco-related disease. In:Φ: Gori, G.B., Bock, F.G. (Editors). *Banbury Report 3—A Safe Cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 341–351.

(220) RISSANEN, V., ROMO, M., SILTANEN, P. Prehospital sudden death from ischaemic heart disease. A postmortem study. *British Heart Journal* 40(9): 1025–1033, September 1978.

(221) ROBERTSON, T.L., KATO, H., GORDON, T., KAGAN, A., RHOADS, G.G., LAND, C.E., WORTH, R.M., BELSKY, J.L., DOCK, D.S., MIYANISHI, M., KAWAMOTO, S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Coronary heart disease risk factors in Japan and Hawaii. *American Journal of Cardiology* 39(2): 244–249, February 1977.

(222) ROBERTSON, T.L., KATO, H., RHOADS, G.G., KAGAN, A., MARMOT, M., SYME, S.L., GORDON, T., WORTH, R.M., BELSKY, J.L., DOCK, D.S., MIYANISHI, M., KAWAMOTO, S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. *American Journal of Cardiology* 39(2): 239–243, February 1977.

(223) ROGOT, E. Cardiorespiratory disease mortality among British and Norwegian migrants to the United States. *American Journal of Epidemiology* 108(3): 181–191, September 1978.

(224) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213–222, May-June 1980.

(225) ROSENBERG, H.M., KLEBBA, A.J. Trends in cardiovascular mortality with a focus on ischemic heart disease: United States, 1950–1976. Paper presented at the meeting of the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, October 24–25, 1978. In: Havlik, R.J., Feinleib, M., Thom, T., Kramer, B., Sharrett, A.R., Garrison, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication No. 79–1610, May 1979, pp. 11–41.

(226) ROSENBERG, L., HENNEKENS, C.H., ROSNER, B., BELANGER, C., ROTHMAN, K.J., SPEIZER, F.E. Oral contraceptive use in relation to nonfatal myocardial infarction. *American Journal of Epidemiology* 111(1): 59–66, January 1980.

(227) ROSENBERG, L., SHAPIRO, S., KAUFMAN, D.W., SLONE, D., MIETTINEN, O.S., STOLLEY, P.D. Cigarette smoking in relation to the risk of myocardial infarction in young women. Modifying influence of age and predisposing factors. *International Journal of Epidemiology* 9(1): 57–63, March 1980.

(228) ROSENBERG, L., SLONE, D., SHAPIRO, S., KAUFMAN, D., STOLLEY, P.D., MIETTINEN, O.S. Noncontraceptive estrogens and myocardial infarction in young women. *Journal of the American Medical Association* 244(4): 339–342, July 25, 1980.

(229) ROSENMAN, R.H., BRAND, R.J., JENKINS, C.D., FRIEDMAN, M., STRAUS, R., WURM, M. Coronary heart disease in the Western Collaborative Group study. Final followup experience of 8 1/2 years. *Journal of the American Medical Association* 233(8): 872–877, August 25, 1975.

(230) ROSS, R. Atherosclerosis: A problem of the biology of arterial wall cells and their interactions with blood components. *Arteriosclerosis* 1(5): 293–311, September/October 1981.

(231) ROSS, R.K., PAGANINI-HILL, A., MACK, T.M., ARTHUR, M., HENDERSON, B.E. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet* 1(825): 858–860, April 18, 1981.

(232) ROYAL COLLEGE OF PHYSICIANS. *Smoking Or Health.* A report of the Royal College of Physicians, London, Pitman Medical, 1978, 128 pp.

(233) SALONEN, J.T. Stopping smoking and long-term mortality after acute myocardial infarction. *British Heart Journal* 43(4): 463–469, April 1980.

(234) SALONEN, J.T. Oral contraceptives, smoking, and risk of myocardial infarction in young women. A logitudinal population study in eastern Finland. *Acta Medica Scandinavica* 212(3): 141–144, 1982.

(235) SALONEN, J.T., PUSKA, P. Relation of serum cholesterol and triglycerides to the risk of acute myocardial infarction, cerebral stroke and death in eastern Finnish male population. *International Journal of Epidemiology* 12(1): 26–31, March 1983.

(236) SAMUELSON, W., WILLIAMS, R.R., MANESS, A.T. Accuracy of death certificates in Utah for myocardial infarction. (Submitted for publication.)

(237) SCHEIDT, S.S. Angina pectoris: Pathophysiology, precipitating factors, prognosis, and therapy. *Cardiovascular Reviews & Reports* 4(1): 83–90, January 1983.

(238) SCHLANT, R.C., FORMAN, S., STAMLER, J., CANNER, P.L. The natural history of coronary heart disease: Prognostic factors after recovery from myocardial infarction in 2,789 men. The 5-year findings of the Coronary Drug Project. *Circulation* 66(2): 401–414, August 1982.

(239) SCHOENENBERGER, J.C. Smoking change in relation to changes in blood pressure, weight, and cholesterol. *Preventive Medicine* 11(4): 441–453, July 1982.

(240) SCHROLL, M., HAGERUP, L.M. Risk factors of myocardial infarction and death in men aged 50 at entry. A ten-year prospective study from the Glostrup population studies. *Danish Medical Bulletin* 24(6): 252–255, December 1977.

(241) SEVERI, S., DAVIES, G., MASERI, A., MARZULLO, P., L'ABBATE, A. Long-term prognosis of "variant" angina with medical treatment. *American Journal of Cardiology* 46(1): 226–232, August 1980.

(242) SHAPIRO, S., ROSENBERG, L., SLONE, D., KAUFMAN, D.W., STOLLEY, P.D., MIETTINEN, O.S. Oral contraceptive use in relation to myocardial infarction. *Lancet* 1(8119): 743–747, April 7, 1979.

(243) SLONE, D., SHAPIRO, S., KAUFMAN, D.W., ROSENBERG, L., MIETTINEN, O.S., STOLLEY, P.D. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *New England Journal of Medicine* 305(8): 420–424, August 20, 1981.

(244) SLONE, D., SHAPIRO, S., ROSENBERG, L., KAUFMAN, D.W., HARTZ, S.C., ROSSI, A.C., STOLLEY, P.D., MIETTINEN, O.S. Relation of cigarette smoking to myocardial infarction in young women. *New England Journal of Medicine* 298(23): 1273–1276, June 8, 1978.

(245) SOLBERG, L.A., STRONG, J.P. Risk factors and atherosclerotic lesions. A review of autopsy studies. *Arteriosclerosis* 3(3): 187–198, May-June 1983.

(246) SORLIE, P.D., GARCIA-PALMIERI, M.R., COSTAS, R., CRUZ-VIDAL, M., HAVLIK, R. Cigarette smoking and coronary heart disease in Puerto Rico. *Preventive Medicine* 11(3): 304–316, May 1982.

(247) SPAIN, D.M., BRADESS, V.A., MATERO, A., TARTER, R. Sudden death due to coronary atherosclerotic heart disease. Age, smoking habits, and recent thrombi. *Journal of the American Medical Association* 207(7): 1347–1349, February 17, 1969.

(248) SPAIN, D.M., BRADESS, V.A., MOHR, C. Coronary atherosclerosis as a cause of unexpected and unexplained death. An autopsy study from 1949–1959. *Journal of the American Medical Association* 174(4): 384–388, September 24, 1961.

(249) SPAIN, D.M., SIEGEL, H., BRADESS, V.A. Women smokers and sudden death. The relationship of cigarette smoking to coronary disease. *Journal of the American Medical Association* 224(7): 1005–1007, May 14, 1973.

(250) SPARROW, D., DAWBER, T.R., COLTON, T. The influence of cigarette smoking on prognosis after a first myocardial infarction. A report from the Framingham study. *Journal of Chronic Diseases* 31(6/7): 425–432, 1978.

(251) STAMLER, J., EPSTEIN, F.H. Coronary heart disease: Risk factors as guides to preventive action. *Preventive Medicine* 1(1–2): 27–48, March 1972.

(252) STROBEL, M., GSELL, O. Mortalitat in Bezeihung Zum Tabakrauchen. 9 Jahre Beobachtungen bei Arzten in der Schweiz. [Mortality in relation to tobacco smoking. Nine years of observation in Swiss physicians.] *Helvetica Medica Acta* 32(6): 547–592, December 1965.

(253) SUGRUE, D.D., THOMPSON, G.R., OAKLEY, C.M., TRAYNER, I.M., STEINER, R.E. Contrasting patterns of coronary atherosclerosis in normocholesterolaemic smokers and patients with familial hypercholesterolaemia. *British Medical Journal* 283(6303): 1358–1360, November 21, 1981.

(254) TALBOTT, E., KULLER, L.H., DETRE, K., PERPER, J. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. *American Journal of Cardiology* 39(6): 858–864, May 26, 1977.

(255) TALBOTT, E., KULLER, L.H., PERPER, J., MURPHY, P.A. Sudden unexpected death in women: Biologic and psychosocial origins. *American Journal of Epidemiology* 114(5): 671–682, November 1981.

(256) THOMAS, P.C., CADY, L.D., O'CONNELL, E.R., BISCHOFF, D.P., KERSHNAR, R.K. Heart disease risk factors in Los Angeles County safety personnel. *Journal of Occupational Medicine* 21(10): 683–687, October 1979.

(257) TOWNSEND, J.L., MEADE, T.W. Ischaemic heart disease mortality risks for smokers and non-smokers. *Journal of Epidemiology and Community Health* 33(4): 243–247, December 1979.

(258) TYROLER, H.A. Epidemiologic studies of cardiovascular disease in three communities of the southeastern United States. In: Kessler, I.I., Levin, M.L. (Editors). *The Community as an Epidemiologic Laboratory. A Casebook of Community Studies* Baltimore, Johns Hopkins University Press, 1970, pp. 100–122.

(259) TYROLER, H.A., GLUECK, C.J., CHRISTENSEN, B., KWITEROVICH, P.O., Jr. Plasma high-density lipoprotein cholesterol comparisons in black and white populations. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-99—IV-107, November 1980.

(260) UESHIMA, H., IIDA, M., SHIMAMOTO, T., KONISHI, M., TANIGAKI, M., NAKANISHI, N., TAKAYAMA, Y., OZAWA, H., KOJIMA, S., KOMACHI, Y. High-density lipoprotein-cholesterol levels in Japan. *Journal of the American Medical Association* 247(14): 1985–1987, April 9, 1982.

(261) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking for Women: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980, 359 pp.

(262) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHHS Publication No. (PHS)81–50156, 1981, 252 pp.

(263) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79–50066, 1979, 1136 pp.

(264) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM)71–7513, 1971, 458 pp.

(265) VAN GENT, C.M., VAN DER VOORT, H., HESSEL, L.W. High-density lipoprotein cholesterol, monthly variation and association with cardiovascular risk factors in 1000 forty-year-old Dutch citizens. *Clinica Chimica Acta* 88(1): 155–162, August 15, 1978.

(266) VAN GENT, C.M., VAN DER VOORT, H., STEGERHOEK, C.J., STYBLO, K. Reduced high-density lipoprotein in women aged 40–41 using oral contraceptives. *Lancet* 1:1221-1223, June 10, 1978.

(267) VESSEY, M.P., McPHERSON, K., JOHNSON, B. Mortality among women participating in the Oxford/Family Planning Association contraceptive study. *Lancet* 2(8041): 731–733, October 8, 1977.

(268) VLIETSTRA, R.E., FRYE, R.L., KRONMAL, R.A., SIM, D.A., PHIL, M., TRISTANI, F.E., KILLIP, T. Risk factors and angiographic coronary artery disease: A report from the Coronary Artery Surgery Study (CASS). *Circulation* 62(2): 254–261, August 1980.

(269) WAHL, P., WALDEN, C., KNOPP, R., HOOVER, J., WALLACE, R., HEISS, G., RIFKIND, B. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. *New England Journal of Medicine* 308(15): 862–867, April 14, 1983.

(270) WALD, N.J. Cigarette smoking and coronary heart disease in young women. In: Oliver, M.F. (Editor). *Coronary Heart Disease in Young Women.* Edinburgh, Churchill Livingstone, 1978, pp. 43–58.

(271) WALD, N., HOWARD, S., SMITH, P.G., KJELDSEN, K. Association between atherosclerotic diseases and carboxyhaemoglobin levels in tobacco smokers. *British Medical Journal* 1(5856): 761–765, March 31, 1973.

(272) WATERS, D.D., HALPHEN, C., THEROUX, P., DAVID, P.-R., MIZGALA, H.F. Coronary artery disease in young women: Clinical and angiographic features and correlation with risk factors. *American Journal of Cardiology* 42(1): 41–47, July 1978.

(273) WEAVER, W.D., LORCH, G.S., ALVAREZ, H.A., COBB, L.A. Angiographic findings and prognostic indicators in patients resuscitated from sudden cardiac death. *Circulation* 54(6): 895–900, December 1976.

(274) WEIR, J.M., DUNN, J.E., Jr. Smoking and mortality: A prospective study. *Cancer* 25(1): 105–112, January 1970.

(275) WERKO, L. Can we prevent heart disease? *Annals of Internal Medicine* 74(2): 278–288, February 1971.

(276) WHITE, P.D. Coronary disease and coronary thrombosis in youth. An analysis of 4 cases under the age of thirty years, 21 cases under the age of forty years, and 138 cases under the age of fifty years. *Journal of the Medical Society of New Jersey* 32(10): 596–605, October 1935.

(277) WHYTE, H.M. The relative importance of the major risk factors in atherosclerotic and other diseases. *Australian and New Zealand Journal of Medicine* 6: 387–393, 1976.

(278) WILHELMSEN, L. Risk factors for disease according to population studies in Göteborg, Sweden. Paper presented at Skandia International Symposia, September 23–25, 1980. In: Bostrom, H., Ljungstedt, N. (Editors). *Medical Aspects of Mortality Statistics.* Skandia International Symposia. Stockholm, Almquist and Wiksell International, 1981, pp. 73–88.

(279) WILHELMSEN, L., BENGTSSON, C., ELMFELDT, D., VEDIN, A., WILHELMSSON, C., TIBBLIN, G., LINDQVIST, O., WEDEL, H. Multiple risk prediction of myocardial infarction in women as compared with men. *British Heart Journal* 39(11): 1179–1185, November 1977.

(280) WILLETT, W.C., HENNEKENS, C.H., BAIN, C., ROSNER, B., SPEIZER, F.E. Cigarette smoking and non-fatal myocardial infarction in women. *American Journal of Epidemiology* 113(5): 575–582, May 1981.

(281) WILLETT, W., HENNEKENS, C.H., CASTELLI, W., ROSNER, B., EVANS, D., TAYLOR, J., KASS, E.H. Effects of cigarette smoking on fasting triglyceride, total cholesterol, and HDL-cholesterol in women. *American Heart Journal* 105(3): 417–421, March 1983.

(282) WILLETT, W., STAMPFER, M.J., BAIN, C., LIPNICK, R., SPEIZER, F.E., ROSNER, B., CRAMER, D., HENNEKENS, C.H. Cigarette smoking, relative weight, and menopause. *American Journal of Epidemiology* 117(6): 651–658, June 1983.

(283) WINKELSTEIN, W., Jr., REKATE, A.C. Age trend of mortality from coronary artery disease in women and observations on the reproductive patterns of those affected. *American Heart Journal* 67(4): 481–488, April 1968.

(284) WORTH, R.M., KATO, H., RHOADS, G.G., KAGAN, A., SYME, S.L. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: Mortality. *American Journal of Epidemiology* 102(6): 481–480, December 1975.

(285) WYNDER, E.L., LEMON, F.R. Cancer, coronary artery disease and smoking. A preliminary report on differences in incidence between Seventh-Day Adventists and others. *California Medicine* 89(4): 267–272, October 1958.

SECTION 4. CEREBROVASCULAR DISEASE

Introduction

Death rates from stroke have been declining in developed countries since the 1920s (*28*). Between 1968 and 1975 there was a sharp decline in the age-adjusted mortality rates from coronary heart disease, cerebrovascular diseases, and all major cardiovascular diseases among U.S. white and nonwhite males and females (*50*). As shown in Table 1, the decrease is close to 33 percent for stroke.

Additional major reductions in disability and death from stroke can come largely from preventive measures, not from further innovations in treatment of the completed catastrophe. Formulation of a preventive program is greatly aided by an understanding of the epidemiology of cerebrovascular disease, including the chain of circumstances leading to its occurrence, the identity of vulnerable subgroups of the population, the existence of modifiable predisposing factors, and the natural history of the disease.

Magnitude of the Problem

Cerebrovascular diseases, both ischemic and hemorrhagic, are a public health problem of major proportions. They constitute the third leading cause of death, after coronary heart disease and cancer, and are responsible for 9 percent of all deaths in the United States (*33*). There are about 1.8 million stroke victims in the United States, and about a half-million new events occur each year; there are approximately 200,000 deaths annually in the United States from strokes. In the Framingham study it was estimated that the chances of suffering a stroke before age 70 are 1 in 20. The incidence was found to double in each successive decade after age 45. Although stroke incidence becomes substantial only after age 65, 20 percent of strokes occur before that age. In men, the average annual incidence of atherothrombotic brain infarction is only one-third that of myocardial infarction, with stroke incidence lagging behind myocardial infarction by more than 10 years. In women, on the other hand, brain infarction incidence and myocardial infarction incidence are virtually identical (*56*). The reasons that brain infarction is manifested later in life than CHD in men and exhibits little male predominance are unclear. In the United States, stroke mortality is higher among blacks than among whites, and the difference decreases with age.

The Stroke Entity

There are three major specific forms of cerebrovascular diseases: (1) cerebral insufficiency associated with transient blood flow deficiencies; (2) cerebral infarction caused either by the blocking of a vessel by an embolism or by thrombosis; and (3) cerebral hemorrhage, including parenchymal and subarachnoid. The terms "stroke"

TABLE 1.—Percentage of change in mortality rates of causes of death in persons aged 35 to 74, by sex and color, United States, 1968–1976

Cause of death	Percentage of change				
	White men	White women	Nonwhite men	Nonwhite women	All
Coronary heart disease	-21.0	-26.5	-30.7	-39.1	-24.3
Cerebrovascular diseases	-30.6	-30.4	-43.7	-47.1	-32.7
Major cardiovascular diseases	-20.9	-26.1	-33.2	-40.7	-24.6
All causes	-15.3	-16.4	-24.8	-32.7	-17.3

SOURCE: Stamler (*50*).

and "cerebral vascular accident" are nonspecific; they refer to a variety of clinical entities and are usually used in reference to syndromes accompanying ischemic or hemorrhagic lesions.

The underlying process of a stroke may be an atheroma (i.e., fatty deposit in the inner lining of an artery wall), thrombosis, embolism, a bleeding disorder, a developmental anomaly, an aneurysm, inflammation, failure of flow, or increased blood viscosity. The chief causes of cerebral ischemia are atherothrombosis and embolism. Intracranial hemorrhage is generally due to hypertensive intracerebral hemorrhage, rupture of a saccular aneurysm, or bleeding from an arteriovenous malformation. A cerebral embolism usually originates in the heart, particularly when atrial fibrillation, rheumatic valvular deformity, myocardial infarction with a mural thrombus, or a valve prosthesis is present; it may also arise from ulcerated atheroma in the carotid, vertebrobasilar, or middle cerebral arteries. The main trunk of the middle cerebral artery and its branches are the most common sites for the formation of intracranial thrombosis.

The reliability of stroke diagnoses and case ascertainment in diverse populations has presented problems for epidemiological and clinical research. With the fairly recent development of new technology such as computer-assisted tomography, however, the accuracy and the quality of differential diagnosis as to type of stroke are improving. It is unlikely that any single etiology or set of risk factors applies equally to all types of stroke. Atherothrombotic brain infarction is the most common variety of stroke, accounting for about 59 percent of the total number of strokes in the Framingham population (*56*).

Cardiovascular Risk Factors

Since the underlying pathologic features of atherosclerosis in the cerebral, cardiac, and peripheral circulation are virtually identical,

it is not unexpected to find that they share a number of precursors. Although some significant differences in their impact exist, there are a number of modifiable risk factors common to brain and myocardial infarction (*22*). In fact, when five major cardiovascular risk factors (systolic blood pressure, serum cholesterol, glucose intolerance, cigarette smoking, and electrocardiogram–left ventricular hypertrophy (ECG-LVH)) are considered jointly as a cardiovascular risk profile, they are actually more highly predictive of brain infarction than of coronary heart disease (*24*). The top decile of multivariate risk using this profile identifies half the strokes evolving in the Framingham population, compared with only 25 percent of the coronary events (*22*). However, for cerebrovascular disease, systolic blood pressure and ECG-LVH were the chief determinants of this multivariate predictive capacity. In addition to these risk predictors, various cardiac impairments such as coronary heart disease, cardiac failure, and atrial fibrillation are major predisposing factors (*55*). Cigarette smoking, which is a major predictor for coronary heart disease, has been less consistently predictive for cerebrovascular disease; but nevertheless appears to play a significant role among men at younger ages.

Hypertension

A consistent finding in epidemiologic studies is that elevated blood pressure is the most important risk factor for stroke. This seems to apply for virtually all varieties of stroke (*56*). It is the key risk factor for intracerebral hemorrhage, occlusive cerebral vascular disease, and perhaps subarachnoid hemorrhage (*28*). About 50 to 60 percent of strokes occur in the 20 percent of the population with definite hypertension. Hypertension predisposes powerfully to stroke at all ages and in both sexes, and even mild elevations in blood pressure double the risk. The stroke risk for isolated systolic hypertension is substantial, and the exclusive use of diastolic pressure to judge the risk in the elderly with systolic hypertension can be misleading. No component of blood pressure, including the pulse pressure, mean arterial pressure, or diastolic pressure, is more closely related to stroke incidence than systolic pressure (*25*). Also, lability of the pressure has not been shown to reduce the risk, and it is not safe to use the lowest pressure recorded to determine whether treatment is indicated.

Blood Lipids

Lipids and their lipoprotein vehicles, closely linked to coronary disease incidence, are of uncertain importance for stroke. Neither cholesterol nor triglyceride levels have any predictive value beyond age 55, when strokes are common, and partition of the serum total cholesterol into its atherogenic low density lipoprotein (LDL) and

protective high density lipoprotein (HDL) components does not clarify the role of cholesterol in stroke as it does for coronary heart disease in advanced age (*11*). In women there is actually a paradoxical, strong negative association of brain infarction incidence with LDL cholesterol. This inverse relationship to atherogenic cholesterol has also been noted in Japanese men and for intracerebral hemorrhage (*19*). Hence, further clarification is needed.

Glucose

Atherothrombotic brain infarction incidence is increased threefold in diabetics. In contrast to coronary heart disease, the impact of impaired glucose tolerance does not diminish with advancing age and is not greater for women than for men. The effect of diabetes mellitus is independent of other risk factors, but is greatly influenced by coexistent hypertension or cardiac disease (*23*).

Cardiac Disease

Even if asymptomatic, cardiac changes such as ECG-LVH, cardiac enlargement on X-ray, atrial fibrillation, coronary disease, cardiac failure, or rheumatic heart disease powerfully predispose to the occurrence of strokes. ECG-LVH is the most powerful ECG predictor. Atrial fibrillation, chronic as well as intermittent, increases stroke risk sixfold, and when accompanied by rheumatic heart disease, seventeenfold (*55*). Although each contributes independently to risk, coexistent hypertension further augments the risk associated with any cardiac impairment.

Environmental Factors

Few modifiable environmental contributors to stroke incidence have been convincingly demonstrated. The demonstrated association of obesity with stroke incidence appears to derive mainly from the higher blood pressure and glucose intolerance that it promotes. Physical activity is weakly and inconsistently related to stroke incidence (*55*). The apparent influence of coffee intake disappears on adjustment for coexistent alcohol and cigarette use. Alcohol seems to be associated with an increased risk of stroke in some studies, possibly because of higher blood pressure in alcohol users.

Cigarette Smoking

The contribution of cigarette smoking to the incidence of stroke may vary depending on the type of stroke or clinical manifestation of cerebrovascular disease. The evidence for such a relationship suggests that smoking is more strongly associated with premature (i.e., before age 55) and nonfatal strokes than with fatal strokes (*22*).

With 16 years of followup data on 293,000 insured U.S. veterans, Rogot and Murray (*43*) reported that 653 excess stroke deaths were associated with cigarette smoking, producing a mortality ratio of 1.47. Earlier, with 8.5 years of followup, Kahn (*21*) had found stroke mortality to be 1.4 times higher in smokers and rates to increase with amount smoked. In the more recent study, a slight dose–response relationship was found for both current and ex-smokers, with mortality ratios lower among former smokers than among current smokers. Mortality ratios for stroke were near unity for smokers of only cigars or pipes—1.07 and 0.99, respectively (*43*). A study of 54,460 men employed in British industries revealed no relationship between the cigarette habit and stroke mortality over 3 years, but demonstrated a threefold excess coronary mortality (*3*).

Kuller (*28*), in a review of the epidemiology of stroke, concluded that there was no consistent evidence of a relationship of cigarette smoking to stroke in several population and case–control studies. Data after 24 years of followup in the Framingham study showed no overall statistically significant relationship between the incidence of atherothrombotic brain infarction (ABI) and cigarette smoking among males. The stroke incidence was lower in nonsmoking males only between the ages of 45 and 54, and no clear dose–response was evident (*56*). In a comparison of stroke prevalence—not specified as to type—among Japanese in Japan, Hawaii, and California, preliminary analyses revealed positive correlations between stroke and increased blood pressure, ECG-LVH, and cigarette smoking for all ages (*20*). Paffenbarger et al. (*37*) found no relationship between cigarette smoking and stroke in a 22-year followup of 3,686 longshoremen.

In an earlier study of chronic diseases among male former students at Harvard, Paffenbarger and Wing (*38*) noted a slight excess of nonfatal stroke among those who had smoked during college. They also found that hypertension, overweight, and short stature were predisposing characteristics for stroke in later life. The data must be interpreted with some caution, however, because they were abstracted from existing school records and the smoking information was not collected in a standardized manner. In a Canadian retrospective study (*1*), a relative risk of 2.4 ($p < 0.001$) was found for stroke and smoking, but these results are also subject to potential bias in the recording of the smoking history.

Hammond and Horn (*15*) studied the relationship between smoking and disease among 187,783 white men, 50 to 69 years old, followed from May 1952 through October 1955. Of the 11,870 deaths during this period, 1,050 were from cerebral vascular lesions. A statistically significant mortality ratio of 1.30 was found for smokers and a dose–response relationship was apparent.

TABLE 2.—Mortality ratios for cerebrovascular disease related to smoking, United States, 1969[1]

Cigarettes/day	Mortality ratios (N=4,099), by age			
	40–49	50–59	60–69	70–79
	Males			
Never smoked	1.00	1.00	1.00	1.00
1–9	2.79	1.95	1.30	0.95
10–19	1.14	1.48	1.44[2]	0.92
20–30	2.21	2.03	1.62	1.22
>40	1.64	2.40	1.72	0.68[2]
	Females			
Never smoked	1.00	1.00	1.00	1.00
1–9	1.50	1.26	1.26	0.83
10–19	2.60	2.70	2.15	0.57[2]
20–30	2.90	2.67	1.83	1.28
>40	5.70[2]	3.52[2]	—	—

[1] Population included 358,584 males and 445,875 females, 40–79 years of age at entry. Data collected from questionnaire and 6-year followup of death certificate.

[2] Based on only five to nine deaths.

SOURCE: Hammond and Garfinkel (*14*).

In a large-scale prospective study of male British physicians, Doll and Hill (*8*) found that the results differed somewhat between the 10th and 20th year of followup. A stroke mortality ratio of 1.2 was found for smokers at the 10-year followup, with no dose–response relationship evident. After 20 years of followup, a relative risk for cerebral thrombosis of 1.52 was found for heavy smokers and a strong dose–response relationship was apparent (*9*).

In an analysis of the 1,094 deaths that occurred among female British physicians who had been followed for 22 years, Doll et al. (*7*) found no effect of smoking on mortality from cerebral thrombosis; however, there were only 68 such deaths.

The American Cancer Society studied prospectively more than a million men and women enrolled in 1959, following them for 13 years. With 6 years of followup, mortality ratios for cerebral vascular disease were found to be increased among male and female smokers compared with nonsmokers, with the highest ratios evident among the 40- to 49-year-olds (Table 2). The excess risk was not present in either sex past age 70. There was no significant dose–response relationship (*13, 14*).

A study of the differences in mortality ratios by the type of cigarette smoked (*29*) and a later analysis of data from the American Cancer Society study indicated lower mortality ratios from stroke among males who smoked low tar and nicotine or filtered cigarettes than among smokers of higher tar and nicotine cigarettes or of "plain" cigarettes (*6*). No such differences were found among

females. A study conducted by the Tobacco Research Council in England showed mortality ratios that were lower, but not significantly so, among smokers of lower tar and nicotine cigarettes (*6*).

In 1965, Ostfeld began a prospective study among random samples of the elderly in Cook County, Illinois, to determine variables associated with stroke. They found that stroke-prone persons can be identified even among the elderly. Stroke risk was higher among the blacks and among persons with preexisting cardiovascular disease, transient ischemic attacks (TIAs), diabetes mellitus, or hypertensive cardiovascular disease. Cigarette smoking was, however, unrelated to any class of stroke in the elderly, with or without preexisting cardiovascular precursors (*36*).

Kimura (*26*) reviewed the results of six prospective studies of cardiovascular disease in Japan and found a correlation of cigarette smoking with myocardial infarction when accompanied by abnormalities in serum cholesterol and blood pressure; no relationship of cigarette smoking to stroke was noted. Okada et al. (*34*) studied stroke prospectively in Japanese men 40 years old or older residing in two rural communities and found relative risks of intracerebral hemorrhage and brain infarction among nonsmokers that were not statistically significantly lower than those in smokers.

In an 8-year prospective study of a random sample of 35- to 59-year-olds in two counties in eastern Finland, age, blood pressure, diabetes mellitus, and previous stroke were found to be predictive of stroke incidence in both men and women. Cigarette smoking and serum triglyceride levels were found to be positively associated with stroke among men, but not among the women (*47*). In an effort to predict coronary heart disease and other mortality rates, Menotti et al. (*32*) analyzed 14 CHD risk factors using a multiple logistic function model. The study included 1,524 men between 40 and 59 from two rural areas in Italy who were measured for all 14 risk factors upon entry. After 15 years, 37 men had had a stroke. Of the 14 risk factors considered, age and blood pressure were the only factors found to be significantly associated with stroke risk, ranking 1 and 2, respectively. Smoking ranked third for predicting stroke, but was not statistically significant.

In a retrospective study (*16*) of 126 stroke patients and 212 matched controls in Tilburg, Holland, a significantly increased risk of stroke associated with cigarette smoking was not found. Hypertension was found to be related to stroke, and the risk was age dependent, being strongest among the younger patients.

An investigation in Finland (*10*) of 128 men and 85 women under 50 years of age with ischemic stroke revealed 1.5 times as many cigarette-smoking men and three times as many cigarette-smoking women in the stroke group as in the Finnish population of the same age. Hypertension, abnormal electrocardiographic findings, and oral

contraceptive use in women were also shown to increase risk. In a large prospective study (*40*) of women under 55 years of age in California who were followed for 6.5 years, cigarette smoking increased the risk of subarachnoid hemorrhage 5.7 times and use of oral contraceptives increased it 6.5 times. The relative risk was 21.9 among women who both smoked and used the pill compared with nonsmoking nonusers. In a case–control study (*4*) involving 12 university hospitals, 598 nonpregnant women with strokes between age 15 and 44 were identified. Compared with controls, current use of oral contraceptives was considerably higher in women with thrombotic strokes (ninefold) and somewhat higher in women with hemorrhagic strokes. It was also found that 74 percent were current or past smokers. In an investigation of 75 hemiplegics aged 18 to 50 years, Steinmann (*51*) found that cardiac disease and hypertension were the predominant risk factors. In men, but not in women, heavy smoking was a risk factor.

Further confirming the general impression that cigarette smoking is a stroke risk factor in young men are the results of three case–control studies. Among 100 male stroke patients, aged 40 to 69, Koch et al. (*27*) found a relative risk of 11.2 for smokers of more than 20 cigarettes a day. In a study (*30*) of 56 male and 34 female patients under 66 years of age with cerebral hemorrhage or infarction, significantly more stroke patients than their matched controls were found to be smokers, and more smoked at least a pack of cigarettes a day. Other factors predisposing to stroke in this study population were high blood pressure, oral contraceptive use, and a family history of stroke, plus cerebral neoplasm and thrombocytopenia. In another study (*52*), among 39 male and 28 female ischemic stroke patients, cigarette smoking was found significantly more frequently among male cases than among matched controls. In the young females, use of oral contraceptives was the predominant risk factor.

Haberman et al. (*12*) summarized mortality and incidence studies dealing with smoking and stroke (Tables 3 and 4). They pointed out that the relationship between smoking and cerebrovascular disease is not a uniform finding of the epidemiologic studies of this disease process. The authors cautioned that the studies are not strictly comparable because of variations in methodologies, but they suggested that an association between smoking and stroke may exist but be age dependent. An age dependency is suggested by the Framingham and Paffenbarger studies.

Transient Ischemic Attacks

Some evidence connects cigarette smoking with transient ischemic attacks (TIA). In a 6-year followup for TIA of 7,895 men aged 45 to 68 years in the Honolulu heart study (*41*), prior cigarette smoking was

TABLE 3.—Results of stroke incidence studies

Study	Type[1]	Date	Disease[2]	Relationship between stroke and smoking[3]	Approximate relative risk
Hiroshima	P	1958–64	CI	None	-
Washington	P	1961–71	Stroke	None	0.9
			CI	None	0.8–1.1
Framingham	P	1949–73	ABI	Yes. Not sig	1.1–2.7 (males)
Manitoba	R	1970–71	CI	Yes. Sig?	2.4
Rural Japan	P	1964–70	Stroke	Yes. Not sig	1.9–2.7
Harvard	P	1916–66	Nonfatal CI	Yes. Sig	1.6
Walnut Creek	P	1969–76	SAH	Yes. Sig	5.7
Queen Square	R	1965–78	Aneurysm	Yes. Sig?	3.8

[1] P denotes prospective; R denotes retrospective.
[2] CI: cerebral infarction; ABI: atherothrombotic brain infarction; SAH: subarachnoid hemorrhage.
[3] ? denotes doubt about the study design.
SOURCE: Haberman et al. (*12*).

TABLE 4.—Results of stroke mortality studies

Name	Type[1]	Date	Relationship between stroke and smoking	Approximate mortality ratio
Longshoremen	P	1951–69	None	1.1
Washington	P, R	1962–71	None	0.9
Harvard	P	1916–66	Yes	2.1
Dorn	P	1954–62	Yes	1.3–1.9
British doctors (10 year)	P	1951–61	None	1.2
British doctors (20 year)	P[2]	1951–71	Yes	1.1–1.5
American Cancer Society	P	1959–65	Yes	1.3–2.8

[1] P denotes prospective; R denotes retrospective.
[2] Based on cerebral thrombosis only.
SOURCE: Haberman et al. (*12*).

associated with TIA, even in multivariate analysis taking other risks into account. However, Ostfeld et al. (*35*) found conflicting results.

Subarachnoid Hemorrhage

A retrospective study (*2*) of patients with subarachnoid hemorrhage demonstrated an association with cigarette smoking. In this study, smoking was estimated to increase the risk of a subarachnoid hemorrhage almost fourfold in both sexes. In the Walnut Creek contraceptive study this was confirmed, with a 5.7-fold increased risk compared with nonsmokers (*39*). Also, in a 6.5-year followup of this cohort of 16,759 white middle-class women aged 18 to 54, cigarette smoking was associated with a fivefold to sevenfold relative risk of subarachnoid hemorrhage and also with a 4.8-fold risk for other strokes (*40*).

Smoking Cessation

Controlled clinical trial data measuring the effect of smoking cessation on cerebrovascular disease are not available; observational studies have been published. In the 16-year followup of 293,000 insured veterans (*43*), specific causes of death were studied in relation to smoking status. Mortality ratios for ex-smokers were found to be much lower than for current smokers. For stroke, the mortality risk for the ex-smoker rapidly returned to the nonsmoker rate after the cessation of smoking. Koch et al. (*27*) found an increased risk of stroke in young patients that was not detectable in ex-smokers after 1 year.

Oral Contraceptives

Oral contraceptives (OCs) have been widely used for more than 20 years, and many reports suggest that women who use them are at increased risk of stroke (*4, 5, 18, 44, 53, 54*). Firm, undistorted prospective data on the risk of cigarette smoking in women taking OCs are sparse, owing to the generally low incidence of stroke in women of childbearing age. Reliance is placed chiefly on retrospective data subject to unavoidable selective bias or on multicenter prospective data based on small numbers of events. Such data as exist strongly suggest a synergistic effect of smoking and oral contraceptives that may be related to "hemorrhagic stroke" (*42, 46*).

In 1969, the Walnut Creek Contraceptive Drug Study began a long-term study of the effects of OC use on the health of women aged 18 to 54 at study initiation. After 6.5 years of followup, Petitti and Wingerd (*39*) analyzed the data from 15,260 women. The authors found relative risks associated with OC use of 6.5 and 7.6 for subarachnoid hemorrhage and thromboembolism, respectively. The risk of subarachnoid hemorrhage for smokers was 5.7 times that for nonsmokers; the relative risk of subarachnoid hemorrhage for women who smoked and used oral contraceptives was 21.9. Among the small number of ex-users, past use significantly increased the risk of subarachnoid hemorrhage, but not of other vascular diseases (*39*). In another study, cigarette smoking in itself was evidently not a demonstrable risk factor for stroke among women, even at an early age (*42*).

In a two-part review article, Stadel (*48, 49*) indicates that OC use multiplies, rather than adds to, the risk of age and other factors in the development of myocardial infarction (MI) and stroke. On the basis of a total of only 31 cases reported in two studies and 134 reported in a third, Stadel (*49*) further indicates that current and past use of OCs appears to increase the risk of subarachnoid hemorrhage in women near age 35 or older (*17*). Stadel suggests that the risk of cardiovascular disease among current users of oral

TABLE 5.—Annual death rate for oral contraceptive users related to age, duration of use, and smoking habits

User characteristic	Annual death rate
Age group	
15–34 years	1 per 20,000
35–44 years	1 per 3,000
45–49 years	1 per 700
Duration of use	
< 5 years	1 per 8,000
> 5 years	1 per 2,000
Smoking habit	
Nonsmoker	1 per 10,000
Smoker	1 per 3,000

SOURCE: McQueen (*31*); Royal College of General Practitioners (*44*).

contraceptives is related to the estrogen and progestogen content of the pill.

A large prospective study in England (46,000 British women) found that both the incidence and the mortality rates of a variety of diseases, including cerebrovascular disease, were increased among users of oral contraceptives versus nonusers (*45*). The number of stroke deaths in the Royal College of General Practitioners (RCGP) study was small; thus, risk estimates were subject to error. Women over 35 and women who smoked and took oral contraceptives were found to be at substantially higher risk than were nonsmokers and nonusers of OCs.

Additional analysis of the RCGP study including followup through 1976 showed that current or previous users of oral contraceptives had a standardized mortality rate for cerebrovascular disease 4.7 times that of controls. Increases in total death rates were found among older women, women who had used the pill for 5 or more years, and women who smoked cigarettes (*44*) (Table 5).

Results from a case–control study conducted by the Collaborative Group for the Study of Stroke in Young Women (*5*) showed that cigarette smoking and the use of oral contraceptives were independent risk factors for subarachnoid hemorrhage; the relative risk was 2.6 for smokers and 4.1 for users of OCs. When a heavy smoker also took oral contraceptives, the risk increased to 6.1 or 7.6, depending upon the control group used for comparison. In an earlier report, the same group (*4*) reported that risk of cerebral ischemia or thrombosis was approximately nine times greater among women using oral contraceptives than among nonusing controls. They also reported

lower incidence rates among black women than among white women and that more of the cases than of the controls were or had been regular smokers.

The data suggest that cigarette smokers who use oral contraception are at significantly increased risk of stroke and that this risk may result from a synergistic interaction between cigarette smoking and the use of oral contraceptives.

Preventive Implications

Declining trends in stroke mortality and the marked geographic variation suggest that cerebrovascular disease may not be an inevitable consequence of aging or of genetic makeup. High risk candidates can be identified using a general cardiovascular risk profile. There is as yet no conclusive evidence that intervening to lower lipids, reduce overweight, provide exercise, treat diabetes mellitus, or stop cigarette smoking will in fact reduce stroke risk. However, former cigarette smokers appear to have a lower risk of stroke than do continuing smokers.

The key to stroke prevention is early, vigorous, sustained control of hypertension and the cardiac impairments that escalate the risk. Cigarette smoking cessation may also play a role, particularly in young male stroke candidates or in women using oral contraceptives.

Summary

A preventive approach to stroke is imperative because central nervous system damage often leads to an irreversible functional deficit. Less than a third of stroke victims have symptoms warning of the impending stroke. The similarity of factors predisposing to stroke and those increasing susceptibility to coronary heart disease and congestive heart failure indicates that vascular disease of the brain is part of a larger problem of cardiovascular disease. The measures indicated for prevention of stroke include those recommended for prevention of coronary heart disease, occlusive peripheral arterial disease, and congestive heart failure. Hypertension is clearly the major contributor to stroke incidence. Cigarette smoking also contributes, especially in younger populations, and may be important because of its demonstrated relationship to coronary heart disease and congestive heart failure, which powerfully contribute to stroke risk. Cigarette smoking cessation is indicated as part of a comprehensive program of risk factor modification to avoid atherosclerotic cardiovascular disease, including stroke.

Women cigarette smokers experience an increased risk for subarachnoid hemorrhage; the use of both cigarettes and oral contraceptives appears to synergistically increase this risk.

Conclusions

1. Data from numerous prospective mortality studies have shown an association between cigarette smoking and cerebrovascular disease. This risk is most evident in the younger age groups, and the effect diminishes with increasing age, with little or no effect noted after age 65. No consistent dose–response effect has been demonstrated.
2. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage. However, the use of both cigarettes and oral contraceptives greatly increases the risk for subarachnoid hemorrhage among women.

References

(1) ABU-ZEID, H.A.H., CHOI, N.W., MAINI, K.K., HSU, P.-H., NELSON, N.A. Relative role of factors associated with cerebral infarction and cerebral hemorrhage. *Stroke* 8(1): 106–112, January-February 1977.

(2) BELL, B.A., SYMON, L. Smoking and subarachnoid haemorrhage. *British Medical Journal* 1(6163): 577–582, March 3, 1979.

(3) BRETT, G.Z., BENJAMIN, B. Smoking habits of men employed in industry, and mortality. *British Medical Journal* 3(5610): 82–85, July 13, 1968.

(4) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraception and increased risk of cerebral ischemia or thrombosis. *New England Journal of Medicine* 288(17): 871–878, April 26, 1973.

(5) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraceptives and stroke in young women. Associated risk factors. *Journal of the American Medical Association* 231(7): 718–722, February 17, 1975.

(6) DEAN, G., LEE, P.N., TODD, G.F., WICKEN, A.J. *Report on a Second Retrospective Mortality Study in North-East England.* Part I: Factors related to mortality from lung cancer, bronchitis, heart disease and stroke in Cleveland County, with a particular emphasis on the relative risks associated with smoking filter and plain cigarettes. Tobacco Research Council, Research Paper 14, London, 1977, 95 pp.

(7) DOLL, R., GRAY, R., HAFNER, B., PETO, R. Mortality in relation to smoking: 22 years' observations on female British doctors. *British Medical Journal* 280(6219): 967–971, April 5, 1980.

(8) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. *British Medical Journal* 1(5395): 1399–1410, May 30, 1964.

(9) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 2(6051): 1525–1536, December 25, 1976.

(10) FOGELHOLM, R., AHO, K. Ischaemic cerebrovascular disease in young adults. I. Smoking habits, use of oral contraceptives, relative weight, blood pressure and electrocardiographic findings. *Acta Neurologica Scandinavica* 49(4): 415–427, 1973.

(11) GORDON, T., KANNEL, W.B., CASTELLI, W.P., DAWBER, T.R. Lipoproteins, cardiovascular disease, and death. The Framingham study. *Archives of Internal Medicine* 141(9): 1128–1131, August 1981.

(12) HABERMAN, S., CAPILDEO, R., ROSE, F.C. Smoking: A risk factor for stroke? In: Greenhalgh, R.M. (Editor). *Smoking and Arterial Disease.* Bath, Great Britain, Pitman Press, 1981, pp. 17–28.

(13) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 127–204.

(14) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167–182, August 1969.

(15) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159–1172, March 8, 1958.

(16) HERMAN, B., LEYTEN, A.C.M., Van LUIJK, J.H., FRENKEN, C.W.G.M., OPDECOUL, A.A.W., SCHULTE, B.P.M. An evaluation of risk factors for stroke in a Dutch community. *Stroke* 13(3): 334–339, May-June, 1982.

(17) INMAN, W.H.W. Oral contraceptives and fatal subarachnoid hemorrhage. *British Medical Journal* 2(6202): 1468–1470, December 1, 1979.

(18) JICK, H., PORTER, J., ROTHMAN, K.J. Oral contraceptives and nonfatal stroke in healthy young women. *Annals of Internal Medicine* 89(1): 58–60, July 1978.

(19) KAGAN, A., POPPER, J.S., RHOADS, G.G. Factors related to stroke incidence in Hawaii Japanese men: The Honolulu heart study. *Stroke* 11(1): 14–21, January-February 1980.

(20) KAGAN, A., POPPER, J.S, RHOADS, G.G., TAKEYA, Y., KATO, H., GOODE, G.B., MARMOT, M. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: Prevalence of stroke. In: Scheinberg, P. (Editor). *Cerebrovascular Diseases.* New York, Raven Press, 1976, pp. 267–277.

(21) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8 and one-half years of observation. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 1–125.

(22) KANNEL, W.B. Epidemiologic studies on smoking in cerebral and peripheral vascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker.* Volume 1. Proceedings of the Third World Congress on Smoking and Health, New York, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 257–274.

(23) KANNEL, W.B., McGEE, D.L. Diabetes and cardiovascular disease. The Framingham study. *Journal of the American Medical Association* 241(19): 2035–2038, May 11, 1979.

(24) KANNEL, W.B., McGEE, D.L., GORDON, T. A general cardiovascular risk profile: The Framingham study. *American Journal of Cardiology* 38(1): 46–51, July 1976.

(25) KANNEL, W.B., WOLF, P.A., McGEE, D.L., DAWBER, T.R., McNAMARA, P., CASTELLI, W.P. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. *Journal of the American Medical Association* 245(12): 1225–1229, March 27, 1981.

(26) KIMURA, N. Epidemiological studies in Japan on smoking and cardiovascular disease. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). *Health Consequences, Education, Cessation Activities and Governmental Action.* Volume II. Proceedings of the Third World Conference on Smoking and Health, New York, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)77–1413, 1977, pp. 185–192.

(27) KOCH, A., REUTHER, R., BOOS, R., REUTHER, E., MOERL, H. Risikofaktoren bi cerebralen Durchblutungsstoerungen. [Risk factors of cerebral blood circulation disorders.] *Verhandlungen der Deutschen Gesellschaft für Innere Medizin* 83: 1773–1776, 1977.

(28) KULLER, L.H. Epidemiology of stroke. In: Schoenberg, D.S. (Editor). *Neurological Epidemiology: Principles and Clinical Applications.* Advances in Neurology. Volume 19. New York, Raven Press, 1978, pp. 281–311.

(29) LEE, P.N., GARFINKEL, L. Mortality and type of cigarette smoked. *Journal of Epidemiology and Community Health* 35(1): 16–22, March 1981.

(30) MacKAY, A., NIAS, B.C. Strokes in young and middle-aged: Consequences to the family and to society. *Journal of the Royal College of Physicians of London* 13(2): 106–112, 1979.

(31) McQUEEN, E.G. Hormonal steroid contraceptives: A further review of adverse reactions. *Current Therapeutics* 19: 176–200, October 1978.

(32) MENOTTI, A., CONTI, S., GIAMPAOLI, S., MARIOTTI, S., SIGNORETTI, P. Coronary risk factors predicting coronary and other causes of death in fifteen years. *Acta Cardiologica* 35(2): 107–120, 1980.

(33) NATIONAL CENTER FOR HEALTH STATISTICS. *Monthly Vital Statistics Report.* U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, National Center for Health Statistics. DHHS Publication No. (PHS) 80–1120, Volume 29, No. 1, Supplement, April 28, 1980.

(34) OKADA, H., HORIBE, H., OHNO, Y., HAYAKAWA, N., AOKI, N. A prospective study of cerebrovascular disease in Japanese rural communities, Akabane and Asahi. Part I: Evaluation of risk factors in the occurrence of cerebral hemorrhage and thrombosis. *Stroke* 7(6): 599–607, November-December 1976.

(35) OSTFELD, A.M., SHEKELLE, R.B., KLAWANS, H.L. Transient ischemic attacks and risk of stroke in an elderly poor population. *Stroke* 4(6): 980–986, November-December 1973.

(36) OSTFELD, A.M., SHEKELLE, R.B., KLAWANS, H., TUFO, H.M. Epidemiology of stroke in an elderly welfare population. *American Journal of Public Health* 64(5): 450–458, May 1974.

(37) PAFFENBARGER, R.S., Jr., BRAND, R.J., SHOLTZ, R.I., JUNG, D.L. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. *American Journal of Epidemiology* 108(1): 12–18, July 1978.

(38) PAFFENBARGER, R.S., Jr., WING, A.L. Chronic disease in former college students. XI. Early precursors of nonfatal stroke. *American Journal of Epidemiology* 94(6): 524–530, December 1971.

(39) PETITTI, D.B., WINGERD, J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid hemorrhage. *Lancet* 2(8083): 234–236, July 29, 1978.

(40) PETITTI, D.B., WINGERD, J., PELLEGRIN, F., RAMCHARAN, S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *Journal of the American Medical Association* 242(11): 1150–1154, September 14, 1979.

(41) RHOADS, G.G., POPPER, J.S., KAGAN, A., YANO, K. Incidence of transient cerebral ischemic attack in Hawaii Japanese men. The Honolulu heart study. *Stroke* 11(1): 21–26, January-February 1980.

(42) RINEHART, W., PIOTROW, P.T. Oral contraceptives—Update on usage, safety, and side effects. *Population Reports* Series A(5): 133–186, 1979.

(43) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213–222, May-June 1980.

(44) ROYAL COLLEGE OF GENERAL PRACTITIONERS. Oral contraceptive study. Mortality among oral contraceptive users. *Lancet* 2(8041): 727–731, October 8, 1977.

(45) ROYAL COLLEGE OF GENERAL PRACTITIONERS. *Oral Contraceptives and Health.* An interim report from the Oral Contraceptive Study of the Royal College of General Practitioners. Manchester, England, Pitman Publishing Corporation, 1974, 100 pp.

(46) ROYAL COLLEGE OF GENERAL PRACTITIONERS. Oral contraceptive study. Further analysis of mortality in oral contraceptive users. *Lancet* 1(8219): 541–546, March 7, 1981.

(47) SALONEN, J.T., PUSKA, P., TUOMILEHTO, J., HOMAN, K. Relation of blood pressure, serum lipids, and smoking to the risk of cerebral stroke: A longitudinal study in Eastern Finland. *Stroke* 13(3): 327–333, May-June 1982.

(48) STADEL, B.V. Oral contraceptives and cardiovascular disease (First of two parts). *New England Journal of Medicine* 305(11): 612–618, September 10, 1981.

(49) STADEL, B.V. Oral contraceptives and cardiovascular disease (Second of two parts). *New England Journal of Medicine* 305(12): 672–677, September 17, 1981.

(50) STAMLER, J. What is happening with coronary heart disease in the United States? In: Hayase, S., Murao, S., MacArthur, C. (Editors). *Cardiology.* Proceedings of the VIII World Congress of Cardiology, Tokyo, September 17–23, 1978.

(51) STEINMANN, B. Zur Pathogenese der Apoplexie im Alter unter 50 Jahren. [On the pathogenesis of apoplexy in persons below 50 years of age.] *Schweizerische Medizinische Wochenschrift* 99(31): 1098–1106, 1969.

(52) TURNHEIM, M., HAVELEC, L., HEISS, W.-D., SUMMER, K. Eigenarten ischaemischer insulte bei jungen Ernachsensen. [Characteristic features of ischemic strokes in young adults]. *Weiner Klinische Wochenschrift* 89(4): 106–110, 1977.

(53) VESSEY, M.P., DOLL, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. *British Medical Journal* 2(5599): 199–205, April 27, 1968.

(54) VESSEY, M.P., DOLL, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. *British Medical Journal* 2(5658): 651–657, June 14, 1969.

(55) WOLF, P.A., DAWBER, T.R., KANNEL, W.B. Heart disease as a precursor of stroke. In: Schoenberg, D.S. (Editor). *Neurological Epidemiology: Principles and Clinical Applications. Advances in Neurology.* Volume 19, New York, Raven Press, 1978, pp. 567–577.

(56) WOLF, P.A., DAWBER, T.R., THOMAS, H.E., Jr., KANNEL, W.B. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology* 28(10): 973–977, October 1978.

SECTION 5. ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE AND AORTIC ANEURYSM

Atherosclerotic Peripheral Vascular Disease

Introduction

The peripheral arteries include those branches of the aorta supplying the upper and lower extremities and the abdominal viscera. Most peripheral arterial occlusive disease is due to atherosclerosis, although other conditions such as fibromuscular dysplasia, muscular entrapment, cystic adventitial degeneration, and arteritis may cause obstruction of the peripheral arteries. Symptomatic atherosclerotic peripheral vascular disease (ASPVD) occurs most often in the vessels of the lower extremities. The anatomic location of such disease is usually classified according to the major arterial segments involved, including aortoiliac, femoro-popliteal, and tibioperoneal artery occlusive disease. Occlusive lesions of the origins of visceral arteries commonly involve the renal arteries and the mesenteric arteries, including the celiac and superior and inferior mesenteric arteries.

With many asymptomatic patients, peripheral arterial occlusive disease can be detected on physical examination. Symptomatic patients are usually classified according to the severity of presenting complaints; for example, patients may be classified as suffering intermittent claudication (leg pain brought on by exercise and relieved by rest), ischemic rest pain, or, the most severe complaint, tissue necrosis, including gangrene or ischemic ulceration. Patients with renal artery occlusive disease may present with severe and uncontrollable hypertension, although such patients may respond to medical treatment for hypertension. Patients with arterial occlusive disease of the mesenteric arteries may present with acute ischemia of the intestine, due to thrombosis or embolization, or with more chronic symptoms of pain aggravated by eating and weight loss.

The diagnosis of peripheral arterial occlusive disease can usually be made from the history and physical examination, including the evaluation of peripheral arterial pulsations and detection of arterial bruits. However, more accurate and objective diagnosis of peripheral arterial occlusive disease is possible with noninvasive diagnostic techniques, particularly Doppler ultrasound or plethysmography. Arteriography is reserved for patients with symptoms sufficient to make them candidates for surgery, and is not usually required for the diagnosis of peripheral arterial occlusive disease.

The majority of patients with peripheral arterial disease may be candidates for medical therapy such as exercise regimens and reduction of known risk factors through cessation of smoking, control of diabetes mellitus, dietary measures to control hyperlipidemia and obesity, and medical management of hypertension. Intensive foot hygiene and avoidance of trauma are additional important medical measures for patients with lower extremity ASPVD. The

newly developed treatment of balloon dilatation (percutaneous transluminal angioplasty) may be used to restore pulsatile flow for severely symptomatic patients. Surgical therapy is required in only about 10 percent of the patients with advanced arterial occlusive disease. One surgical approach is arterial reconstruction, usually involving endarterectomy or bypass with vein or prosthetic grafts of diseased segments. Sympathectomy is infrequently used, but it may be helpful in patients with cutaneous ischemia, for whom restoration of pulsatile flow is not possible. Amputation of limbs with advanced arterial occlusive disease that cannot be remedied by surgical reconstruction remains in use, but it is required by only about 5 percent of all patients presenting with peripheral arterial occlusive disease.

Risk Factors for Peripheral Arterial Occlusive Disease

The most powerful risk factor predisposing to atherosclerotic peripheral arterial occlusive disease is cigarette smoking (*47*); in fact, the rarity of peripheral arterial occlusive disease in patients who have never smoked was noted by Eastcott as early as 1962 (*23*). The epidemiologic evidence linking cigarette smoking to atherosclerotic peripheral arterial occlusive disease is discussed in detail below.

Several studies have suggested hyperlipoproteinemia as a risk factor contributing to atherosclerotic peripheral arterial occlusive disease. The type of hyperlipoproteinemia and the degree of association with peripheral vascular disease appear to be different, however, from the hyperlipoproteinemia associated with coronary artery disease. Zelis et al. (*92*) reported that patients with Type III hyperlipoproteinemia are particularly susceptible to the development of peripheral vascular disease, and they noted objective improvement in the peripheral circulation with medical treatment of this disorder. Greenhalgh et al. (*30*) reported that fasting serum lipid concentrations were abnormally high in 44 percent of a consecutive series of 116 patients with proven peripheral vascular disease. In 39 percent of the patients the serum triglyceride level was raised, and in 15 percent the serum cholesterol level was increased. Ballantyne and Laurie (*5*) evaluated 353 consecutive patients with peripheral vascular disease and showed a predominance of Type IV hyperlipoproteinemia in males, but a predominance of Type IIa hyperlipoproteinemia in females. Patients with peripheral vascular disease and Type IIa or Type IIb hyperlipoproteinemia were more likely to have associated coronary artery disease. Eighty-four percent of the patients were cigarette smokers, with the majority smoking more than 10 cigarettes daily. There was no relationship between cigarette consumption and the occurrence of hyperlipoproteinemia. However, Farid et al. (*25*) found that in 122 patients with angiographically proved peripheral arterial occlusive disease, heavy

smoking seemed to be associated with an unexpectedly high proportion of an abnormal lipid pattern: 43 percent of the males exhibited Type IV hyperlipoproteinemia. Lawrie et al. (*51*) surveyed 4,477 healthy males and females in the west of Scotland and found a high prevalence of hyperlipoproteinemia of Type II and Type IV. Hyperlipoproteinemia occurred more frequently in survivors of myocardial infarction, but also occurred, though to a lesser extent, in patients with peripheral vascular disease.

Olsson and Eklund (*57*) evaluated 160 men and 123 women with digit plethysmoraphy and found that most atherogenic lipoprotein abnormalities associated with disease of the lower extremities involved the relatively triglyceride-rich part of the low density lipoprotein (LDL) fraction and the relatively cholesterol-rich part of the very low density lipoprotein (VLDL) fraction. These authors found a deleterious influence of smoking even in the preclinical stage of peripheral vascular disease. Davignon et al. (*18*) evaluated 114 French Canadian patients with angiographically proved peripheral vascular disease. The severity of atherosclerosis correlated positively with plasma triglyceride concentration, but cigarette smoking was the risk factor most frequently found in patients with peripheral vascular disease. In contrast, Erikson et al. (*24*) did not find a positive correlation between arteriographic changes in 30 patients with intermittent claudication and serum concentrations of lipids and lipoproteins. Trayner et al. (*80*) compared 32 patients with peripheral vascular disease to control subjects. The vascular disease study group had a significantly higher incidence of hypertriglyceridemia, more marked for the males, and had lower levels of high density lipoproteins (HDL) than did the control subjects. The study group also had a twofold higher prevalence of cigarette smoking than control subjects. Control patients who smoked also had lower levels of HDL than those who did not smoke. Phillips et al. (*61*) also established a relationship between an increase of VLDL triglyceride and cigarette smoking, while HDL cholesterol decreased with cigarette smoking.

Hypertension is associated not only with coronary and cerebrovascular disease, but also with peripheral arterial occlusive disease (*46*). Larson et al. (*50*) established an interaction of hypertension and hypercholesterolemia in an experimental study of mongrel dogs, suggesting that the combination of these two risk factors produces alterations in lipid composition in the canine aorta that appears to be geometric rather than arithmetic in nature. However, Stehbens (*74*) claimed that epidemiologic studies are less conclusive than experimental studies in establishing the relationship of risk factors in atherosclerosis. He postulated that local hemodynamics associated with hemodynamic stress, rather than the level of lipid intake, is the

principal factor governing the accumulation of lipid in the vessel wall.

It is clear that multiple risk factors have been associated with atherosclerosis not only in the coronary and cerebrovascular arterial beds but also in the peripheral circulation. Rosen et al. (*65*) evaluated the association of risk factors in 109 patients with peripheral arterial occlusive disease. The arterial disease was established by clinical and arteriographic examination and classified into three anatomic groups—aortoiliac, combined aortoiliac and femoropopliteal, and femoropopliteal disease. Type IV hyperlipoproteinemia and glucose intolerance were significantly more common in patients with isolated femoropopliteal disease. Cigarette smoking was the most prominent risk factor in all groups, occurring in 90 percent of patients with aortoiliac or combined disease and in 75 percent of patients with femoropopliteal artery disease. The onset of clinical symptoms occurred at an average of 8 to 10 years earlier in smokers than in nonsmokers. Heyden et al. (*35*) established that smoking and coffee drinking interact in affecting LDL and total cholesterol, but coffee drinking alone did not appear to affect blood lipids. Criqui et al. (*16*) reviewed the relationship between cigarette smoking and HDL cholesterol in 2,663 men and 2,553 women aged 20 to 69 years in 10 North American populations of the Lipid Research Clinics Program Prevalence Study. Cigarette smoking was associated with substantially lower levels of HDL cholesterol; this association was dose related. Hulley et al. (*37*) found the same association in a longitudinal study of 301 high-risk males 35 to 57 years of age. After 1 year's intervention on diet, hypertension treatment, and smoking counseling, both smoking frequency and serum thiocyanate were significantly and independently associated with the changing plasma HDL-cholesterol concentration. A relationship linking cigarette smoking and abnormal lipoprotein metabolism comes from the report of Topping et al. (*78*), which found that patients with both Type III hyperlipoproteinemia and cigarette smoking suffer abnormalities of liver metabolism of cholesterol-rich "remnants." Such impaired hepatic metabolism may result in hyperlipoproteinemia and subsequent peripheral vascular disease.

Summary of Epidemiologic Studies

Because peripheral arterial occlusive disease does not pose as severe a mortality threat as coronary artery disease does, there have been fewer major epidemiologic studies of peripheral vascular disease. However, the underlying pathologic lesion, atherosclerosis, remains the same in the two conditions, and there is increasing evidence of an association between peripheral vascular disease and similar lesions in the coronary or cerebrovascular beds. Both clinical and angiographic correlates of peripheral arterial disease with

concomitant coronary artery disease were suggested by the reports of Friedman et al. (*28*), Kuebler et al. (*49*), Silvestre et al. (*72*), and Hertzer et al. (*34*). These reports not only suggest a clinical relationship between peripheral and coronary artery occlusive disease, but also indicate that the perioperative and long-term risks of treatment for peripheral vascular disease are strongly influenced by the presence of concomitant coronary artery disease.

Several publications have extensively reviewed the evidence associating cigarette smoking with peripheral arterial occlusive disease (*81, 82, 83*). Early studies by Juergens et al. (*44*), Begg (*7*), Schwartz et al. (*71*), and Widmer et al. (*87*) documented a much higher prevalence of cigarette smoking (usually exceeding 90 percent) in patients with peripheral arterial occlusive disease, when compared with control patients without vascular disease. Data from the Framingham study (*46*) suggest that cigarette smoking is one of the major risk factors in the development of intermittent claudication (Table 1). Over a 16-year period of followup, a higher total incidence and a higher annual incidence of intermittent claudication were noted in smokers as compared with nonsmokers. This difference was statistically significant for all age groups of both sexes. Using multivariate analysis to control for other risk factors, this relationship of smoking to intermittent claudication became stronger.

Many other investigators have noted a high prevalence of cigarette smoking in patients with peripheral arterial occlusive disease. Tomatis et al. (*77*) found that 98 percent of patients with aortoiliac disease and 91 percent of patients with femoropopliteal disease were cigarette smokers. Astrup et al. (*3*) found a significant correlation between the frequency of severe intermittent claudication and the consumption of more than 15 cigarettes a day in nondiabetic patients with peripheral vascular disease. A significant difference between heavy smokers and other smokers was not found, however, for the development of gangrene. Further, the development of claudication did not vary with the number of years of smoking or the total number of cigarettes consumed in a lifetime. Weinroth and Herzstein (*84*) noted a 50 percent greater incidence of peripheral arterial occlusive disease in diabetics who smoked than in those who did not. Juergens et al. (*44*) followed 520 patients with nondiabetic peripheral arterial occlusive disease, approximately 50 percent of whom continued to smoke despite medical advice to quit. Of those who continued to smoke, approximately 10 percent eventually required amputation, but no amputations were necessary in patients who successfully stopped smoking.

Horowitz et al. (*36*) reported that age was a significant factor in the prevalence of arterial disease, with nearly half of the cases occurring in patients over the age of 70. A higher percentage of patients with

TABLE 1.—Average annual incidence (over 16 years) of intermittent claudication according to cigarette habit at examination

Age at examination and cigarettes smoked per day	Men			Women		
	Subjects at risk [1]	Rate per 10,000		Subjects at risk [1]	Rate per 10,000	
		Actual	Smoothed [2]		Actual	Smoothed [2]
45–54 years	6290	16	15.9	7933	4	3.8
None	2342	6	9.8	4514	3	2.4
Under 20	903	17	13.4	1876	0	4.0
20	1486	30	18.3	1090	9	6.5
Over 20	1523	16	24.9	422	12	10.6
55–64 years	4484	51	51.3	5959	19	19.3
None	2170	28	27.6	4276	19	17.5
Under 20	743	61	43.6	1030	19	21.6
20	879	40	68.7	434	0	26.7
Over 20	670	127	107.9	197	76	33.1
65–74 years	1326	57	56.6	1924	31	31.2
None	790	44	55.2	1541	19	23.6
Under 20	254	98	57.3	266	94	45.3
20	167	90	59.5	79	0	86.5
Over 20	111	0	61.7	29	172	164.2

[1] Numbers of subjects at risk according to cigarettes smoked do not add to totals shown because some subjects are in the unknown category.

[2] The "smoothed" rates are based on the mean of the individual probabilities of development of intermittent claudication in the 2 years following examination, where individual probability is calculated according to cigarette use at examination using the values of the parameters estimated in fitting the logistic function to the occurrence of intermittent claudication in the sex-age group.

NOTE: The trend is significantly different from zero at the 0.05 level for women 65 to 74 years of age and at the 0.01 level for men 55 to 64.

SOURCE: Kannel and Shurtleff (*48*).

arterial disease smoked than did patients without arterial disease. A higher percentage of males than of females had peripheral arterial occlusive disease. De Backer et al. (*21*) likewise noted an increase in intermittent claudication with increasing age, but also found a significant correlation of serum cholesterol, systolic blood pressure, blood glucose, and cigarette smoking in patients with intermittent claudication.

Future epidemiologic studies of peripheral vascular disease must take into account the merits and limitations of the clinical diagnosis of peripheral arterial occlusive disease. Horowitz et al. (*36*) suggest that the judgment of trained paramedical personnel compares favorably with that of physicians in screening large numbers of patients for peripheral vascular disease.

De Backer et al. (*21*) emphasized the importance of using ankle systolic blood pressure measurement with Doppler ultrasound to

objectively screen patients for peripheral arterial occlusive disease. Such useful techniques have been emphasized by Marinelli et al. (*54*) in a large epidemiologic study of vascular disease in patients with diabetes mellitus.

In addition to clinical studies, several autopsy surveys have reported an association between smoking and peripheral atherosclerosis (*59, 60, 66, 67, 75, 89*). Such studies have supported a direct association between smoking and the formation of abdominal aortic fatty streaks, as well as their subsequent conversion to raised lesions.

Most reports of peripheral vascular disease emphasize the predominant occurrence of this disorder in males (*88*). However, diabetes mellitus may predispose females to peripheral arterial occlusive disease in a frequency similar to that of males. Broome et al. (*12*) reported on 15 women with aortoiliac occlusive disease, all of whom were cigarette smokers (mean, 20 cigarettes a day), and none of whom had diabetes mellitus. The temporal trend toward increased smoking by women may significantly increase their risk of peripheral arterial occlusive disease. The Framingham heart study (*47*) found that the incidence of peripheral vascular disease was increased among smokers and that cigarette smoking was as strong an independent risk factor in women as in men. Heavy smokers had a threefold increase in the incidence of peripheral arterial occlusive disease. Weiss (*86*) evaluated 245 women with peripheral arterial occlusive disease. The risk in ex-smokers who had not smoked for 5 years or more was nearly normal, with a risk ratio of 1.06. Patients who had not smoked for 1 to 5 years had a risk ratio of 1.70. Patients who continued to smoke, but smoked less than one pack a day, had a risk ratio of 11.53, and those who smoked more than a pack a day had a risk ratio of 15.56. The risk for arterial occlusive disease was particularly associated with the proximal aortoiliac segment and was less associated with distal or femoral-popliteal artery disease. This study described both a dose–response effect and a benefit following cessation of smoking.

There have been few studies of the association of visceral arterial occlusive disease and cigarette smoking. Mackay et al. (*53*) reported on the correlation of smoking and renal artery stenosis. They found that smoking was nearly twice as common in patients with nonmalignant hypertension associated with renal artery stenosis as in those patients with hypertension of comparable severity without renal artery disease. Previous studies documented that a higher proportion of smokers was noted in patients with malignant hypertension (*10, 39*). Cigarette smoking was present in 20 of 22 patients with malignant hypertension and associated renal artery stenosis (*53*).

Cigarette smoking appears to be the only form of tobacco consumption associated with an increased risk of developing periph-

eral arterial occlusive disease. Smith (*73*) reported that no cases of intermittent claudication were found in patients who used only smokeless tobacco (snuff, chewing tobacco), provided that patients with a history of diabetes mellitus, heavy ethanol intake, or dietary problems were excluded.

Frishman (*29*) reviewed the effects of involuntary smoking on the cardiovascular system. Although levels of carbon monoxide commonly found in cigarette-smoke-filled environments have been demonstrated to decrease exercise tolerance in patients with existing angina pectoris and intermittent claudication, studies are not available to document the role that passive smoking might play in the etiology of atherosclerotic cardiovascular disease (*69*).

Clinical Investigations in Humans

In several studies, the effect of cigarette smoking or the constituents of cigarette smoke on the human peripheral vascular system has been investigated. Cryer et al. (*17*) studied the effects of cigarette smoking, sham smoking, and smoking with adrenergic blockade in 10 subjects. There was a significant increase in the mean plasma norepinephrine and epinephrine levels associated with smoking. The smoking-related increase in pulse rate, blood pressure, blood glycerol, and blood lactate-pyruvate ratio was prevented by adrenergic blockade. These findings were attributed to local norepinephrine release from adrenergic axon terminals within tissues rather than to increments in circulating catecholamines. In experiments comparing cigarettes of varying nicotine content, the subjective recognition of different cigarette brands may influence the results of clinical experiments. Ossip et al. (*58*) have suggested that nicotine extraction filters be used to minimize the within-subject differences due to the recognition of cigarette brand. The influence of the type of beta blocker used in therapy of patients who are cigarette smokers was investigated by Trap-Jensen et al. (*79*). These authors found that the use of a nonselective beta blocker, propranolol, during smoking caused a marked rise in diastolic and mean blood pressure and forearm vascular resistance, due to the blockade of adrenaline-induced vasodilatation, which is mediated by beta-2 receptors in the resistance vessels. Selective beta-1 blockade with atenolol attenuated the systolic blood pressure and the tachycardiac responses induced by cigarette smoking.

Several studies have suggested an association between cigarette smoking and the level of circulating hemoglobin. Castleden et al. (*14*) evaluated 61 male nondiabetic smokers with peripheral artery disease and compared them with age-matched nondiabetic male smokers and nonsmokers admitted for routine inquinal herniorrhaphy. They found a significant association between smoking and hemoglobin levels and a highly significant correlation between

smoking and peripheral vascular disease. In addition, the carboxyhemoglobin generated by smoking was associated with increased platelet adhesiveness, decreased fibrinolytic activity, and increased plasma fibrinogen. Yamori et al. (*91*) suggested that the hematocrit was increased in proportion to the number of cigarettes smoked and that this may be a mechanism for increased mortality rate from cardiovascular diseases in smokers.

Other hematologic effects of cigarette smoke have been observed in blood platelets and with fibrinolysis. Davis and Davis (*19*) studied 18 volunteers to assess the effect of cigarette smoking on platelet aggregation. The smoking of two unfiltered tobacco cigarettes during a 20-minute period resulted in a significant increase in the platelet aggregate ratio. During this time, the mean plasma nonesterified fatty acid concentration remained unchanged. These same authors (*20*) subsequently reported that the increase in the platelet aggregate ratio resulting from smoking two unfiltered cigarettes could be prevented with pretreatment with one aspirin tablet. Janzon and Nilsson (*43*) evaluated the fibrinolytic activity in vein walls among 71 randomly selected heavy smokers and 41 nonsmokers from a population of men born in 1914 residing in Malmö, Sweden. After 12 hours' abstention from tobacco, the smokers were found to have the same fibrinolytic activity as nonsmokers. Smoking six cigarettes during 3 hours increased the fibrinolytic activity in the blood, presumably because of the combined effects of nicotine and carbon monoxide.

Several studies of the effects of smoking on the peripheral circulation have involved noninvasive measurement of limb blood flow using plethysmographic techniques. Janzon (*40*) used a water-filled plethysmograph to study 71 randomly selected heavy smokers and 41 nonsmokers from the study group of men born in 1914 and residing in Malmö, Sweden. The smokers were found to have lower systolic and diastolic arm blood pressure and lower systolic blood pressure in the big toe with greater pressure gradients from the arm to the big toe compared with nonsmokers. During reactive hyperemia, smokers had decreased blood flow and increased peripheral vascular resistance. This same author (*42*) studied the acute effect of smoking on heart rate, blood pressure, and calf blood flow in 20 randomly selected 59-year-old male heavy smokers (more than 15 g of tobacco per day). After smoking two cigarettes, there was a significant increase in blood pressure and heart rate. Blood flow and resistance to blood flow in the calf did not change at rest, but during reactive hyperemia, the resistance to blood flow decreased and calf blood flow increased, an effect attributable to the peripheral vascular effects of nicotine. Janzon (*41*) evaluated 51 randomly selected 59-year-old heavy smokers for changes in peripheral vascular function after smoking cessation of 8 to 9 weeks. He noted an

increase in blood flow during reactive hyperemia in patients who stopped smoking and a decrease in blood flow in patients who continued to smoke. Isacsson (*38*) performed venous occlusion plethysmography on the calf of 809 randomly selected 55-year-old men residing in Malmö, Sweden. Sixty-two percent of the total population examined were cigarette smokers. A history of intermittent claudication was present in 20 subjects, but arterial insufficiency could be clinically demonstrated in only 6 of the 20. Ilio-femoral occlusive disease was found in another eight patients. These patients had a higher prevalence of systolic hypertension, hypercholesterolemia, hypertriglyceridemia, and lipoprotein abnormalities. The amount of smoking was inversely related to the magnitude of the arterial flow capacity in the legs and directly related to the presence of occlusive arterial disease. More ex-smokers had high blood flow capacity than had a low flow capacity. The arterial flow capacity in the legs was reduced in direct proportion to the tobacco consumption per day. Coffman (*15*) used plethysmographic and isotope methods to document cutaneous vasoconstriction, increased skeletal muscle blood flow, and decreased venous distensibility in human subjects after tobacco smoking or nicotine injection.

Recent studies have employed Doppler ultrasound to document changes in blood velocity and transit time following cigarette smoking. Sarin et al. (*68*) noted a reduction in mean digital artery blood flow velocity of 42 plus or minus 6 percent following the smoking of a single cigarette in 10 male volunteers. Lusby et al. (*52*) evaluated the effects of cigarette smoking on hemodynamics in the large and small vessels of patients with peripheral arterial occlusive disease. Using Doppler probes, large vessel response to smoking was evaluated by measurement of pulse transit time delay. Patients with occlusive arterial disease had significant shortening in transit time delay, suggesting a stiffening in the main vessels in response to smoking. Such changes were not seen in control patients without peripheral arterial occlusive disease. A digit pulse volume recorder was used to measure the amplitude of digit pulsation, a measure of small vessel hemodynamics. The digit pulse amplitudes decreased significantly in response to both low and high nicotine cigarettes, and patients tended to self-titrate their nicotine intake. Due to this maintenance of nicotine level, the study failed to demonstrate a benefit on small vessel hemodynamics accompanying a switch from high to low nicotine cigarettes.

Recent studies suggest that tobacco allergy may play a role in the development of the cardiovascular effects of cigarette smoking. Becker and Dubin (*6*) reported that approximately one-third of healthy smoking and nonsmoking volunteers exhibited immediate cutaneous hypersensitivity to a glycoprotein antigen purified from cured tobacco leaves and found in cigarette smoke. Denburg et al.

(22) skin-tested 164 peripheral vascular disease patients with purified tobacco glycoprotein. The authors also performed basophil degranulation tests to assess in vitro reactivity to tobacco glycoprotein. Immediate skin-test hypersensitivity to tobacco glycoprotein was found in 11 percent of patients with angiographically demonstrable peripheral vascular disease; a control group of normal patients was not skin tested. The basophil degranulation test was positive in 60 percent of smokers compared with 24 percent of nonsmokers ($p < 0.01$). Forty-three percent of skin-test-negative and 91 percent of skin-test-positive patients with peripheral vascular disease had a positive basophil degranulation test. Only 3 percent of patients with negative basophil degranulation tests had a positive skin test. The percent of patients with positive skin tests increased in proportion to the severity of angiographic peripheral vascular disease. What role tobacco hypersensitivity may play in the development of peripheral atherosclerosis remains to be elucidated.

A final area of clinical epidemiologic study is the relationship of maternal smoking to the fetal cardiovascular system. Asmussen (2) studied the umbilical artery, umbilical vein, and vessels of the placental villi of newborn children in relation to the maternal smoking history. His studies documented that severe damage to vessel walls is associated with maternal tobacco smoking during pregnancy. These fetal vascular changes may lead to vascular lesions later in life.

Experimental Studies in Animals

In several experimental animal studies, the relationship between cigarette smoking and atherosclerotic peripheral vascular disease has been investigated. Birnstingl et al. (9) evaluated the effect of short-term exposure to carbon monoxide on platelet adhesion in rabbits. In rabbits exposed on several occasions to an atmosphere containing 400 parts per million carbon monoxide for 6 to 14 hours, there was a highly significant increase in platelet stickiness immediately after exposure to carbon monoxide, followed the next day by a significant fall to levels below the preexposure value.

Richardson (62) evaluated the effects of nicotine and tobacco smoke on capillary blood flow in the rat. Red blood cell velocity in single capillaries within the mesenteric tissue of anesthetized rats was evaluated immediately before and after either intravenous injection of nicotine or inhalation of tobacco smoke. Blood velocity changes associated with tobacco exposure were considered to be passive consequences of changes in systemic arterial blood pressure. This study did not evaluate differential effects on various vascular beds of cigarette smoke or nicotine.

Fisher et al. (27) evaluated the effect of exposure of cholesterol-fed rabbits to the smoke of one cigarette daily over an 11- to 13-month

period. The study failed to demonstrate quantitative or qualitative differences in atherosclerosis in the aorta or coronary or visceral arteries or significant changes in serum lipids. Booyse et al. (*11*) administered nicotine in the drinking water of New Zealand white rabbits during a 25-week period. Fasting serum levels of glucose, triglyceride, total cholesterol, and LDL cholesterol were elevated in the nicotine-treated rabbits compared with the controls. However, there was no significant difference between nicotine-treated and control animals in leukocyte, erythrocyte, and platelet counts or in hematocrit or hemoglobin. Endothelial cells from the aortic arch of nicotine-treated animals showed extensive changes, including increased cytoplasmic silver deposition, increased formation of microvilli, and numerous focal areas of "ruffled" endothelium (projections from the cell surfaces).

Marshall et al. (*55*) evaluated the effects in minipigs of exposure to cigarette smoke or varying concentrations of carbon monoxide for 1- to 16-hour periods. Cigarette smoke and short carbon monoxide exposure resulted in adherence of platelets to the endothelium. After longer exposures, microscopic thrombi were found in the vessel walls. Underlying degeneration in the endothelial cells developed upon exposure to carbon monoxide.

Recent investigations have involved the training of subhuman primates to smoke cigarettes in order to assess the effect on the peripheral circulation and hematologic factors. Schwartz et al. (*70*) have summarized data on experiments in baboons taught to smoke cigarettes. Rogers et al. (*63*) reported on 36 young adult male baboons who were fed an atherogenic diet. Twenty-eight baboons were randomly assigned to smoke 43 cigarettes daily, and 18 baboons were taught to puff air under equivalent experimental conditions. The cigarette-smoking baboons demonstrated significantly higher carbon monoxide and thiocyanate concentrations in blood and cotinine concentrations in the urine than did the nonsmoking baboons. There were no significant differences found in serum total cholesterol, VLDL, and LDL cholesterol or triglyceride concentrations in the smokers compared with the controls. Smoking baboons had significantly higher fasting glucose concentrations and lymphocyte counts. Platelet counts, platelet aggregation, food and water intake, and body weight were not significantly different in the two groups. Such experimental models may provide a valuable method to assess the long-term effects of smoking on the peripheral vascular system of primates.

Intervention Studies

There is considerable indirect evidence that cessation of smoking may significantly influence the effect of medical or surgical therapy on peripheral arterial occlusive disease. Unfortunately, the tendency

of some patients with peripheral arteral occlusive disease to continue smoking often defeats the purpose of medical intervention. Thiruvengadam et al. (*76*) evaluated the effect of diseases at different organ sites upon the smoking habit of chronic smokers. A significant reduction or cessation of smoking was observed in subjects with cardiovascular, pulmonary, neoplastic, or gastointestinal disease, diabetes mellitus, or cirrhosis of the liver. Medical advice played a role in the reduction for only 19 percent of the subjects. Other reasons for reduction or cessation of smoking were socioeconomic factors, aggravation of disease, or belief in a possible relationship between smoking and the disease. Only subjects with psychiatric illnesses and peripheral vascular diseases showed no significant reduction in the smoking habit in comparison with the controls. Of 89 subjects with peripheral vascular disease, 12 increased their smoking with the advent of disease. Feinleib and Williams (*26*) emphasized that peripheral vascular disease risk is elevated only in cigarette smokers and not in cigar or pipe smokers. Smokers who quit gradually approach the lower risk of nonsmokers. Birkenstock et al. (*8*) reported on the role of cessation of smoking on the medical therapy of 390 patients with peripheral vascular disease who were either ineligible or unfit to undergo operative treatment. Conservative management included foot hygiene, walking exercise, cessation of smoking, a low cholesterol diet, and vitamin E therapy. Of 277 patients who smoked, 164 were able to stop smoking. Eighty-five percent of patients who stopped smoking showed improvement in symptoms of peripheral vascular disease on the medical regimen, in comparison with only 20 percent who improved among those who continued to smoke. The degree of improvement was greater in ex-smokers than in nonsmokers. No patient with diabetes mellitus who continued to smoke improved under medical management.

Cessation of smoking appears to play an important role in the long-term success of reconstructive arterial surgery. Wray et al. (*90*) recorded a significantly higher rate of late arterial occlusion in patients who had undergone aortofemoral bypass and who persisted in smoking when compared with patients who stopped smoking postoperatively. In 30 patients who continued to smoke, 9 late occlusions occurred, but no occlusions developed in 16 patients who ceased smoking postoperatively. Myers et al. (*56*) reported a retrospective study of 217 patients undergoing aortofemoral (135) or femoropopliteal (107) vascular reconstruction. Patients who stopped smoking or smoked no more than five cigarettes daily after their operation had late patency rates of approximately 90 percent for aortofemoral reconstruction and 80 percent for femoropopliteal vein grafts. Patients who continued to smoke more than five cigarettes daily had a late complication rate approximately three times greater after aortofemoral reconstruction and four times greater after

femoropopliteal vein grafting, compared with ex-smokers. The late patency rate was approximately inversely proportional to the number of cigarettes smoked per day after the operation. The incidence of late complications was not correlated with the number of cigarettes smoked prior to operation. Burgess et al. (*13*) noted that among patients whose below-knee amputation failed to heal, six of seven (85 percent) were cigarette smokers, whereas among those whose distal amputations healed, only half were smokers.

Aortic Aneurysm

Nature of Abdominal Aortic Aneurysm

Abdominal aortic aneurysm refers to the dilatation or expansion of the aortic wall due to degenerative or inflammatory destruction of the components of the wall. The vast majority of abdominal aortic aneurysms are due to atherosclerosis, although other conditions, including infection, trauma, dissection, or inherited metabolic disease (Ehlers-Danlos syndrome) may be causes. The dilatation may involve only a portion of the arterial wall (saccular aneurysm), but most often involves generalized fusiform enlargement of the artery. Most abdominal aortic aneurysms are located distal to the renal arteries and proximal to the aortic bifurcation. Abdominal aortic aneurysms may coexist with aneurysmal changes in the iliac, femoral, or popliteal arteries. Less commonly, an aneurysm may involve the entire aorta, including the suprarenal and descending thoracic aorta (thoracoabdominal aneurysm).

Most abdominal aortic aneurysms are asymptomatic and are discovered incidentally during a physical examination or on X-ray examination of the spine or abdominal organs. Symptoms, such as back pain or shock, are usually associated with the complication of rupture and constitute the main threat of abdominal aneurysm. Less commonly, distal embolization may lead to acute or chronic peripheral arterial occlusive disease. Although palpation of aortic enlargement is the best clinical indicator of abdominal aneurysm, abdominal B-mode ultrasonography is the most accurate noninvasive method to estimate the exact size of the aneurysm. Arteriography is seldom used before an operation unless there is associated occlusive peripheral vascular disease or a suspicion of renovascular hypertension; this is because the arteriogram may often not depict the true size of the aneurysm owing to the mural thrombus contained within the aneurysm. Surgical repair with a prosthetic graft is recommended for all abdominal aortic aneurysms more than 5 cm in diameter unless associated diseases make the operative risk greater than that of the prognosis of the aneurysm. The risk of rupture increases exponentially with the diameter of the aneurysm.

TABLE 2.—Mortality ratios and deaths (n in parentheses)[1] from nonsyphilitic aortic aneurysm related to smoking, prospective studies, United States

Author and year	Number and type of population	Data collection	Followup years	Number of deaths	Cigarettes per day	Pipes	Cigars	Comments
Hammond and Horn 1958 (*32, 33*)	187,783 white males in 9 States, 50–69 years of age	Questionnaire and followup of death certificate	1.5	68	NS[2] ..... 1.00 (25) (expected) SM[2] ..... 2.72 (68) ($p<0.005$)			
Kahn 1966 (*45*)	U.S. male veterans, 2,265,674 person-years	Questionnaire and followup of death certificate	8.5	491	>39 ..... 7.26 (17) NS ..... 1.00 (58) Current cigarettes. 5.24 (234) 1-9 cigarettes/day. 2.12 (13) 10–20 ..... 5.53 (124) 21–39 ..... 5.95 (76)	NS–1.00 (58) SM–1.13 (8)	NS–1.00 (58) SM–2.06 (24)	
Hammond & Garfinkel 1969 (*31*)	358,534 males, 445,875 females, 40–79 years of age at entry	Questionnaire and followup of death certificate	6	337	NS ..... 1.00 1–9 ..... 2.62 10–19 ..... 3.85 20–39 ..... 4.54 >40 ..... 8.00			Data apply only to males, 50–69 years of age
Weir and Dunn 1970 (*85*)	68,153 California male workers, 35–64 years of age at entry	Questionnaire and followup of death certificate	5–8	51	NS ..... 1.00 All ..... 2.64 ±10 ..... 2.44 ±20 ..... 2.88 ≥30 ..... 2.54			SM includes ex-smokers; NS includes pipe and cigar smokers

[1] Unless otherwise specified, disparities between the total number of deaths and the individual categories are due to the exclusion of occasional, miscellaneous, or former smokers.

[2] NS = nonsmokers; SM = smokers.

Summary of Epidemiologic Data

Several large epidemiologic studies have suggested an elevated incidence of death from ruptured abdominal aneurysm in smokers compared with nonsmokers (*31, 32, 33, 45, 85*) (Table 2). Anderson et al. (*1*) analyzed 344 autopsies for causes of death and relationship to smoking history. The male to female ratio was 1.9:1.0, with a smoking incidence of more than double that of the general population. The overall longevity of men was less than that of women. There was an inverse relationship between smoking and longevity. Five diseases that accounted for 39 percent of the deaths of smokers were bronchogenic carcinoma, peptic ulcer, aortic aneurysm, acute myocardial infarction, and centrilobular emphysema. The 15 ruptured abdominal aortic aneurysms were in 13 male and 2 female smoking patients.

Auerbach and Garfinkel (*4*) evaluated atherosclerosis and aneurysm of the aorta relative to smoking habits and age. In 1,412 aortas collected at autopsy from 1965 to 1970 from male patients, there was a direct relationship between the extent of atherosclerotic lesions and both smoking habit and age. The aortic lesions were graded for formation of plaques, ulceration, and calcification. The complexity of the plaques increased with the number of cigarettes smoked and was greater in ex-cigarette smokers and pipe or cigar smokers than in nonsmokers. More extensive alterations were found in the abdominal aorta than in the thoracic aorta. Aneurysms were found eight times more frequently among those smoking one to two packs of cigarettes per day than among nonsmokers. Black subjects showed about one-half the number of aneurysms and fewer extensive atherosclerotic lesions than did white subjects. At ages over 65 years, abdominal aortic aneurysms were found in 11 percent of all men and in 16 percent of the heavy smokers.

Rogot and Murray (*64*) evaluated the smoking relationship to causes of death among U.S. veterans. Over a 16-year period, there was a significant reduction in mortality rate with the number of years of smoking cessation. Aortic aneurysm, along with bronchitis and emphysema and lung cancer, were among the diseases in which substantial excess risk remained even after 20 years' cessation of cigarette smoking.

Conclusions

1. Cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral arterial disease.
2. Smoking cessation plays an important role in the medical and surgical management of atherosclerotic peripheral vascular disease.

3. Death from rupture of an atherosclerotic abdominal aneurysm is more common in cigarette smokers than in nonsmokers.

References

(1) ANDERSON, A.E., Jr., FORAKER, A.G. Smoking, mortality, and sex in a community hospital necropsy population. *Southern Medical Journal* 74(9): 1097–1100, September 1981.

(2) ASMUSSEN, I. Fetal cardiovascular system as influenced by maternal smoking. *Clinical Cardiology* 2(4): 246–256, 1979.

(3) ASTRUP, P., BIORCK, G., BRUNNER, D., FRIEDMAN, M., FROBERG, S.O., GREGG, D.E., GROEN, J.J., GUNN, C.G., HAUSS, W.H., HEYDEN, S., JOKL, E., KEYS, A., LINHART, J.F., McGILL, H.C., NIKKILA, E.A., RICHARD, J.L., RUTSTEIN, D.D., SCHLIERF, G., STAMLER, J., WOLF, S., WYNDER, S. Exercise and smoking. In: Wolf, S. (Editor). *The Artery and the Process of Arteriosclerosis: Measurement and Modification.* The second half of the proceedings of an interdisciplinary conference on fundamental data on reactions of vascular tissue in man, Lindau, West Germany, April 19–25, 1970. New York, Plenum Press, 1972, pp. 119–149.

(4) AUERBACH, O., GARFINKEL, L. Atherosclerosis and aneurysm of the aorta in relation to smoking habits and age. *Chest* 78(6): 805–809, December 1980.

(5) BALLANTYNE, D., LAWRIE, T.D.V. Hyperlipoproteinaemia and peripheral vascular disease. *Clinica Chimica Acta* 47(2): 269–276, August 30, 1973.

(6) BECKER, C.G., DUBIN, T. Tobacco allergy and cardiovascular disease. *Cardiovascular Medicine* 3(8): 851–854, August 1978.

(7) BEGG, T.B. Characteristics of men with intermittent claudication. *Practitioner* 194(1160): 202–207, February 1965.

(8) BIRKENSTOCK, W.E., LOUW, J.H., TERBLANCHE, J., IMMELMAN, E.J., DENT, D.M., BAKER, P.M. Smoking and other factors affecting the conservative management of peripheral vascular disease. *South African Medical Journal* 49(28): 1129–1132, July 5, 1975.

(9) BIRNSTINGL, M.A., BRINSON, K., CHAKRABARTI, B.K. The effect of short-term exposure to carbon monoxide on platelet stickiness. *British Journal of Surgery* 58(11): 837–839, November 1971.

(10) BLOXHAM, C.A., BEEVERS, D.G., WALKER, J.M. Malignant hypertension and cigarette smoking. *British Medical Journal* 1(6163): 581–583, March 3, 1979.

(11) BOOYSE, F.M., OSIKOWICZ, G., QUARFOOT, A.J. Effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. *American Journal of Pathology* 102(2): 229–238, February 1981.

(12) BROOME, A., CHRISTENSON, J.T., EKLOF, B., NORGREN, L., PLATE, G. Aorto-iliac disease in premenopausal women. *Acta Chirurgica Scandinavica* 146(8): 555–557, 1980.

(13) BURGESS, E.M., MATSEN, F.A., III, WYSS, C.R., SIMMONS, C.W. Segmental transcutaneous measurements of PO_2 in patients requiring below-the-knee amputation for peripheral vascular insufficiency. *Journal of Bone and Joint Surgery* 64-A(3): 378–382, March 1982.

(14) CASTLEDEN, W.M., FAULKNER, K., HOUSE, A.K., WATT, A. Haemoglobin, smoking and peripheral vascular disease. *Journal of the Royal Society of Medicine* 74(8): 586–590, August 1981.

(15) COFFMAN, J.D. Tobacco smoking and the peripheral circulation. *Heart Bulletin* 19(5): 89–93, September-October 1970.

(16) CRIQUI, M.H., WALLACE, R.B., HEISS, G, MISHKEL, M., SCHONFELD, G., JONES, G.T.L. Cigarette smoking and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-70—IV-76, November 1980.

(17) CRYER, P.E., HAYMOND, M.W., SANTIAGO, J.V., SHAH, S.D. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *New England Journal of Medicine* 295(11): 573–577, September 9, 1976.

(18) DAVIGNON, J., LUSSIER-CACAN, S., ORTIN-GEORGE, M., LELIEVRE, M., BERTAGNA, C., GATTEREAU, A., FONTAINE, A. Plasma lipids and lipoprotein patterns in angiographically graded atherosclerosis of the legs and in coronary heart disease. *Canadian Medical Association Journal* 116(11): 1245–1250, June 4, 1977.

(19) DAVIS, J.W., DAVIS, R.F. Acute effect of tobacco cigarette smoking on the platelet aggregate ratio. *American Journal of the Medical Sciences* 278(2): 139–143, September–October 1979.

(20) DAVIS, J.W., DAVIS, R.F. Prevention of cigarette smoking-induced platelet aggregate formation by aspirin. *Archives of Internal Medicine* 141(2): 206–207, February 1981.

(21) De BACKER, G., KORNITZER, M., SOBOLSKI, J., DENOLIN, H. Intermittent claudication—Epidemiology and natural history. *Acta Cardiologica* 34(3): 115–124, 1979.

(22) DENBURG, J., BLAJCHMAN, J., GAULDIE, J., HORSEWOOD, P., GILL, G., THOMSON, G., BEATTIE, H., EVANS, G., BIENENSTOCK, J. Hypersensitivity to tobacco glycoprotein in human peripheral vascular disease. *Annals of Allergy* 47(1): 8–13, July 1981.

(23) EASTCOTT, H.H.G. Rarity of lower-limb ischaemia in nonsmokers. *Lancet* 2(7265): 1117, 1962.

(24) ERIKSON, U., ERICSSON, M., PERSSON, R. On the relation between peripheral atherosclerosis and serum lipoproteins. *Upsala Journal of Medical Sciences* 84(1): 95–104, 1979.

(25) FARID, N.R., DICKINSON, P.H., MacNEAL, I.F., ANDERSON, J. Hyperlipoproteinaemia in peripheral arterial disease in the north of England. *Journal of Cardiovascular Surgery* 15(3): 366–372, 1974.

(26) FEINLEIB, M., WILLIAMS, R.R. Relative risks of myocardial infarction, cardiovascular disease and peripheral vascular disease by type of smoking. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker.* Volume 1. Proceedings of the Third World Conference on Smoking and Health, New York, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 243–256.

(27) FISHER, E.R., WHOLEY, M., SHOEMAKER, R. Cigarette smoking and cholesterol atherosclerosis of rabbits. *Archives of Pathology* 98(6): 418–421, December 1974.

(28) FRIEDMAN, S.A., PANDYA, M., GREIF, E. Peripheral arterial occlusion in patients with acute coronary heart disease. *American Heart Journal* 86(3): 415–419, September 1973.

(29) FRISHMAN, W.H. Involuntary smoking: Cardiovascular effects of smoke on nonsmokers. *Cardiovascular Medicine* 4(3): 289–291, 296, March 1979.

(30) GREENHALGH, R.M., ROSENGARTEN, D.S., MERVART, I., LEWIS, B., CALNAN, J.S., MARTIN, P. Serum lipids and lipoproteins in peripheral vascular disease. *Lancet* 2(7731): 947–950, October 30, 1971.

(31) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167–182, August 1969.

(32) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up on 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159–1172, March 8, 1958.

(33) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294–1308, March 15, 1958.

(34) HERTZER, N.R., YOUNG, J.R., KRAMER, J.R., PHILLIPS, D.F., DeWOLFE, V.G., RUSCHHAUPT, W.F., III, BEVEN, E.G. Routiné coronary angiography prior to elective aortic reconstruction. Results of selective myocardial revascularization in patients with peripheral vascular disease. *Archives of Surgery* 114(11): 1336–1344, November 1979.

(35) HEYDEN, S., HEISS, G., MANEGOLD, C., TYROLER, H.A., HAMES, C.G., BARTEL, A.G., COOPER, G. The combined effect of smoking and coffee drinking on LDL and HDL cholesterol. *Circulation* 60(1): 22–25, 1979.

(36) HOROWITZ, O., LONG, E.T., MALAMED, M., TAYLOR, N. Results of screening patients for peripheral vascular disease by paramedical personnel. *Transactions of the American Clinical and Climatological Association* 83: 218–226, October 1970.

(37) HULLEY, S.B., COHEN, R., WIDDOWSON, G. Plasma high-density lipoprotein cholesterol level. Influence of risk factor intervention. *Journal of the American Medical Association* 238(21): 2269–2271, November 21, 1977.

(38) ISACSSON, S.-O. *Venous Occlusion Plethysmography in 55-Year-Old Men: A Population Study in Malmö, Sweden.* Malmö, Sweden, Malmö General Hospital and University of Lund, 1972, 62 pp.

(39) ISLES, C., BROWN, J.J., CUMMING, A.M.M., LEVER, A.F., McAREAVEY, D., ROBERTSON, J.I.S., HAWTHORNE, V.M., STEWART, G.M., ROBERTSON, J.W.K., WARSHAW, J. Excess smoking in malignant-phase hypertension. *British Medical Journal* 1(6163): 579–581, March 3, 1979.

(40) JANZON, L. Smoking and peripheral circulation in 59-year-old men studied with plethysmography and segmental measurements of systolic blood pressure. *VASA: Zeitschrift für Gefässkrankheiten* 4(2): 120–124, 1975.

(41) JANZON, L. Smoking cessation and peripheral circulation: A population study in 59-year-old men with plethysmography and segmental measurements on systolic blood pressure. *VASA: Zeitschrift für Gefässkrankheiten* 4(3): 282–287, 1975.

(42) JANZON, L. The acute effect of smoking on calf blood flow. A plethysmographic study in heavy smokers. *VASA: Zeitschrift für Gefässkrankheiten* 4(3): 278–281, 1975.

(43) JANZON, L., NILSSON, I.M. Smoking and fibrinolysis. *Circulation* 51(6): 1120–1123, June 1975.

(44) JUERGENS, J.L., BARKER, N.W., HINES, E.A., Jr. Arteriosclerosis obliterans: Review of 520 cases with special reference to pathogenic and prognostic factors. *Circulation* 21(2): 188–195, February 1960.

(45) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8 and one-half years of observation. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 1–125.

(46) KANNEL, W.B. Role of blood pressure in cardiovascular morbidity and mortality. *Progress in Cardiovascular Diseases* 17(1): 5–24, July/August 1974.

(47) KANNEL, W.B. Epidemiology studies of smoking in cerebral and peripheral vascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker.* Volume 1. Proceedings of the Third World Conference on Smoking and Health, New York, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 257–274.

(48) KANNEL, W.B., SHURTLEFF, D. The Framingham study. Cigarettes and the development of intermittent claudication. *Geriatrics* 28(2): 61–68, February 1973.

(49) KUEBLER, W., SCHUETZ, E., GRIES, F.A., KLINGER, H., KOSCHINSKY, T., LOOGEN, L., VOGELBERG, K.H. Periphere Arterielle Verschlu Bkrankheit, Angiographisch Nachweisbare Koronarsklerose und Konstellation von "Risikofaktoren" bei Patienten mit Pektanginosen Beschwarden. [Peripheral arterial disease, angiographically demonstrable coronary arteriosclerosis, and "risk factor" constellation in patients with angina.] *Deutsche Medizinische Wochenschrift* 99(44): 2201–2206, November 1, 1974.

(50) LARSON, R.M., McCANN, R.L., HAGEN, P.-O., DIXON, S.H., FUCHS, J.C.A. Effects of experimental hypertension and hypercholesterolemia on the lipid composition of the aorta. *Surgery* 82(6): 794–800, December 1977.

(51) LAWRIE, T.D.V., LORIMER, A.R., BALLANTYNE, D., JUBB, J.S., MORGAN, H.G. The prevalence of hyperlipoproteinaemia in vascular disease. *Postgraduate Medical Journal* 51(Supplement 8): 7–13, 1975.

(52) LUSBY, R.J., BAUMINGER, B., WOODCOCK, J.P., SKIDMORE, R., BAIRD, R.N. Cigarette smoking: Acute main and small vessel hemodynamic responses in patients with arterial disease. *American Journal of Surgery* 142: 169–173, August 1981.

(53) MacKAY, A., BROWN, J.J., CUMMING, A.M.M., ISLES, C., LEVER, A.F., ROBERTSON, J.I.S. Smoking and renal artery stenosis. *British Medical Journal* 2(6193): 770, September 29, 1979.

(54) MARINELLI, M.R., BEACH, K.W., GLASS, M.J., PRIMOZICH, J.F., STRANDNESS, D.E., Jr. Noninvasive testing vs. clinical evaluation of arterial disease. A prospective study. *Journal of the American Medical Association* 241(19): 2031–2034, May 11, 1979.

(55) MARSHALL, M., HESS, H., STAUBESAND, J. Experimentelle Untersuchungen über den Risikofaktor Rauchen. [Experiments on the risk factor smoking.] *VASA: Zeitschrift für Gefässkrankheiten* 7: 389–397, 1978.

(56) MYERS, K.A., KING, R.B., SCOTT, D.F., JOHNSON, N., MORRIS, P.J. The effect of smoking on the late patency of arterial reconstructions in the legs. *British Journal of Surgery* 65(4): 267–271, April 1978.

(57) OLSSON, A.G., EKLUND, B. Studies in asymptomatic primary hyperlipidaemia. *Acta Medica Scandinavica* 198(3): 197–206, 1975.

(58) OSSIP, D.J., ANDRASIK, F., EPSTEIN, L.H. The effect of nicotine extraction filters on pulse rate and vasomotor activity: A methodological note. *Addictive Behaviors* 6(2): 149–152, 1981.

(59) PATEL, Y.C., EGGEN, D.A., STRONG, J.P. Obesity, smoking and atherosclerosis: A study of interassociations. *Atherosclerosis* 36(4): 481–490, August 1980.

(60) PATEL, Y.C., KODLIN, D., STRONG, J.P. On the interpretation of smoking risks in atherosclerosis. *Journal of Chronic Diseases* 33(3): 147–155, 1980.

(61) PHILLIPS, N.R., HAVEL, R.J., KANE, J.P. Levels and interrelationships of serum and lipoprotein cholesterol and triglycerides. *Arteriosclerosis* 1(1): 13–24, January/February 1981.

(62) RICHARDSON, D. Effects of nicotine and tobacco smoke on capillary blood flow in the rat. In: *1975 Symposium on Nicotine and Carbon Dioxide, Proceedings.* Lexington, Department of Physiology and Biophysics, University of Kentucky College of Medicine, June 1977, pp. 89–95.

(63) ROGERS, W.R., BASS III, R.L., JOHNSON, D.E., KRUSKI, A.W., McMAHAN, C.A., MONTIEL, M.M., MOTT, G.E., WILBUR, R.L., McGILL, H.C., Jr. Atherosclerosis-related responses to cigarette smoking in the baboon. *Circulation* 61(6): 1188–1193, June 1980.

(64) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213–222, May-June 1980.

(65) ROSEN, A.J., DePALMA, R.G., VICTOR, Y. Risk factors in peripheral atherosclerosis. *Archives of Surgery* 107(2): 303–308, August 1973.

(66) SACKETT, D.L., GIBSON, R.W., BROSS, I.D.J., PICKREN, J.W. Relation between aortic atherosclerosis and the use of cigarettes and alcohol. An autopsy study. *New England Journal of Medicine* 279(26): 1413–1420, December 26, 1968.

(67) SACKETT, D.L., WINKELSTEIN, W., Jr. The relationship between cigarette usage and aortic atherosclerosis. *American Journal of Epidemiology* 86(1): 264–270, July 1967.

(68) SARIN, C.L., AUSTIN, J.C., NICKEL, W.O. Effects of smoking on digital blood-flow velocity. *Journal of the American Medical Association* 229(10): 1327–1328, September 2, 1974.

(69) SCHIEVELBEIN, H. Zur Grage des Einflusses von Tabakrauch auf die Morbiditat von Nichtrauchern. [The problem of the effect of tobacco smoke on morbidity in nonsmokers]. *Internist* 14(5): 236–243, May 1973.

(70) SCHWARTZ, C.J., McGILL, H.C., Jr., ROGERS, W.R. Smoking and cardiovascular disease. In: Gori, G.B., Bock, F.G. (Editors). *Banbury Report 3—A Safe Cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 81–91.

(71) SCHWARTZ, D., LELLOUCH, J., ANGUERA, G., RICHARD, J.L., BEAUMONT, J.L. Etiologie comparee de l'arteiopathie obliterante des membres inferieurs et de l'arteriopathie coronarienne. [Comparative etiology of lower limb obliterative arteriopathy and of coronary arteriopathy]. *Archives des Maladies du Coeur et des Vaisseaux* 58(Supplement No. 3, Revue de l'Atherosclerose): 24–32, 1965.

(72) SILVESTRE, A., DESA'NETO, A., JOHNSON, J.M., DESSER, K.B., BENCHIMOL, A. Abnormal electrocardiographic responses to exercise in patients referred for noninvasive evaluation of occlusive peripheral arterial disease. *American Journal of Cardiology* 43(4): 713–716, April 1979.

(73) SMITH, J.F. The use of unsmoked tobacco and intermittent claudication. *Journal of the Tennessee Medical Association* 67(11): 913–914, November 1974.

(74) STEHBENS, W.E. The interrelation of hypertension, lipid, and atherosclerosis. *Cardiovascular Medicine* 2(3): 263–277, March 1977.

(75) STRONG, J.P., RICHARDS, M.L. Cigarette smoking and atherosclerosis in autopsied men. *Atherosclerosis* 23(3): 451–476, May/June 1976.

(76) THIRUVENGADAM, K.V., HARANATH, K., PARAMANANDAM, S., AMIRTHALINGAM, K.N., KHURSHEED BEGUM, S.M. Effects of the advent of disease on smoking habit. *Journal of the Indian Medical Association* 69(3): 51–56, August 1, 1977.

(77) TOMATIS, L.A., FIERENS, E.E., VERBRUGGE, G.P. Evaluation of surgical risk in peripheral vascular disease by coronary artiography: A series of 100 cases. *Surgery* 71(3): 429–435, March 1972.

(78) TOPPING, D.L., DWYER, T., WELLER, R.A. Peripheral vascular disease in cigarette smokers and impaired hepatic metabolism of lipoprotein remnants. *Lancet* 2(8052/8053): 1327–1328, December 24 and 31, 1977.

(79) TRAP-JENSEN, J., CARLSEN, J.E., SVENDSEN, T.L., CHRISTENSEN, N.J. Cardiovascular and adrenergic effects of cigarette smoking during immediate non-selective and selective beta adrenoceptor blockade in humans. *European Journal of Clinical Investigation* 9(3): 181–183, 1979.

(80) TRAYNER, I.M., MANNARINO, E., CLYNE, C.A.C., THOMPSON, G.R. Serum lipids and high density lipoprotein cholesterol in peripheral vascular disease. *British Journal of Surgery* 67(7): 497–499, July 1980.

(81) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79–50066, 1979, 1136 pp.

(82) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM)71–7513, 1971, 458 pp.

(83) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1974.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (CDC)74–8704, 1974, 124 pp.

(84) WEINROTH, L.A., HERZSTEIN, J. Relation of tobacco smoking to arteriosclerosis obliterans in diabetes mellitus. *Journal of the American Medical Association* 131(3): 205–209, May 1946.

(85) WEIR, J.M., DUNN, J.E., Jr. Smoking and mortality: A prospective study. *Cancer* 25(1): 105–112, January 1970.

(86) WEISS, N.S. Cigarette smoking and arteriosclerosis obliterans: An epidemiologic approach. *American Journal of Epidemiology* 95(1): 17–25, 1972.

(87) WIDMER, L.K., HARTMANN, G., DUCHOSAL, F., PLECHL, S.-Ch. Risk factors in arterial occlusion of the limbs. *German Medical Monthly* 14(10): 476–479, October 1969.

(88) WILBERT, L. Nikotinkonsum und arterielle verschlusskrankheit. [Consumption of nicotine and occlusive disease]. *Medizinische Klinik* 66(36): 1190–1192, September 3, 1971.

(89) WILENS, S.L., PLAIR, C.M. Cigarette smoking and arteriosclerosis. *Science* 138(3544): 975–977, November 30, 1962.

(90) WRAY, R., DePALMA, R.G., HUBAY, C.H. Late occlusion of aortofemoral bypass grafts: Influence of cigarette smoking. *Surgery* 70(6): 969–973, December 1971.

(91) YAMORI, Y., KIHARA, M., HORIE, R., NOTE, S., TSUNEMATSU, T., FUKASE, M. Epidemiological analysis on the mechanism of cigarette smoking as a risk factor in cardiovascular diseases. *Japanese Circulation Journal* 44(12): 965–970, December 1980.

(92) ZELIS, R., MASON, D.T., BRAUNWALD, E., LEVY, R.I. Effects of hyperlipoproteinemias and their treatment on the peripheral circulation. *Journal of Clinical Investigation* 49(5): 1007–1015, 1970.

SECTION 6. PHARMACOLOGICAL AND TOXICOLOGICAL IMPLICATIONS OF SMOKE CONSTITUENTS ON CARDIOVASCULAR DISEASE

Introduction

Cardiovascular diseases are the leading causes of death in most of the technologically advanced countries of the Western Hemisphere, accounting for approximately half of all deaths annually in the United States (see Appendix A). The most common among these diseases are atherosclerosis and coronary heart disease; their ischemic complications result in increased morbidity and mortality. Coronary heart disease is the leading cause of death in the United States, accounting for two-thirds of all cardiovascular deaths (*96*).

It is generally acknowledged that coronary heart disease is a multifactorial process; that is, a variety of factors are involved in the development and clinical manifestations of this disease. Therefore, it is not a simple task to determine the etiology and time course of atherogenic development. In addition, the study of atherosclerosis is singularly difficult because no model in the experimental animal exactly replicates the human disease in physiological, morphological, and clinical detail. Investigations in human subjects are further limited by the inability to diagnose the disease in preischemic phases (*44*). Most studies of the pathology of cardiovascular diseases (CVD) have been based on autopsies by coroners or on hospital populations in which only a limited fraction of decedents have been examined. Individuals may show considerable variance in the degree of atherosclerosis identified at autopsy, limiting the value of retrospective analysis (*137*).

In 1971, the U.S. Government established the Task Force on Arteriosclerosis to assess research needs and to make recommendations on priorities for future program plans in this area. Most of the recommendations of this task force have been implemented during the past decade, and important advances have been made in basic and clinical research (*96*). Most important, major epidemiological associations of cardiovascular disease risk not only have been established, but also have been supported by examinations of the arterial wall itself, enabling an increased understanding of the basic mechanisms of disease processes.

Research in cell and molecular biology has provided new information about the interaction of blood-borne components, such as cholesterol, with the arterial wall. Basic research regarding this risk will help to increase our understanding of the effects of other circulating components, such as inhaled cigarette smoke constituents, and will elucidate the susceptibility of arterial cells to these effects.

The most firmly established modifiable risk factors for atherosclerotic CVD are hypercholesterolemia, hypertension, and cigarette smoking. In addition to these, diabetes mellitus, lack of exercise, obesity, and type A behavior have all been suggested as contributors to the multifactorial process known as atherogenesis (*82*). The

assessment of any risk factor, such as cigarette smoking, must be made within the constellation of other risks, i.e., susceptibility to disease that is predicted by multifactorial analysis (*53, 82*).

In the case of cigarette smoking, we are faced with an extremely difficult effort in determining direct cause and effect phenomena that are attributable to single factors. Over 4,000 different compounds have been identified in tobacco smoke (*45*), and the determination of the direct or indirect actions of each upon the arterial wall seems an impossible task.

We will attempt, however, to examine the major components believed to be associated with increased risk for CVD and to remember the multiple risk factors that might be associated with the development of cardiovascular dysfunctions in cigarette smokers.

The variety of possible pharmacological and toxicological implications of smoke and its constituents—and the absence of firm proof of what mechanisms are precisely involved in the unequivocal cause and effect relationship between smoking and cardiovascular disease—should not detract from our confidence in the epidemiologically and clinically irrefutable evidence of the cause and effect role of cigarette smoking in contributing importantly toward heart disease.

Tobacco Smoke: Physical Nature and Chemical Composition

Inside the burning cone of a cigarette, a variety of physical and chemical processes occur in an oxygen-deficient, hydrogen-rich environment at temperatures up to 900°C. Two major regions for the smoke formation are primarily observed—the heat-producing combustion zone and the pyrolysis-distillation zone (*11*). The mainstream smoke (MS) is formed during puff drawing; the sidestream smoke (SS) is generated largely by the smoldering of the cigarette between puffs. Throughout this review, data are discussed relating to cigarette smoke generated by smoking machines, unless otherwise noted. The standard machine smoking parameters for cigarettes were primarily developed for comparing smoke yields obtained under identical conditions. Today, these smoking parameters do not reflect the smoking behavior of many of the cigarette smokers and especially not that of smokers of low-yield cigarettes who tend to draw puffs of greater volume more frequently (*64, 68, 145*).

The mainstream smoke of tobacco products represents a very dense aerosol. In the case of a cigarette without a filter tip, it contains about 5×10^9 spherical particles per milliliter. The size of the particles varies between 0.1 and 1.0 μm, with an average diameter of 0.4 μm (*12*). Three to eight percent of the weight of the total mainstream smoke of a cigarette without a filter tip is attributable to the particulate matter. The remainder consists of vapor phase components with nitrogen (50 to 70 percent), oxygen (10

TABLE 1.—Approximate number of smoke compounds identified in some major compound classes

Compound class	Number identified
Amides, imides, lactones	237
Carboxylic acids	227
Lactones	150
Esters	474
Aldehydes	108
Ketones	521
Alcohols	379
Phenols	282
Amines	196
N-Heterocyclics	921
Hydrocarbons	755
Nitriles	106
Anhydrides	11
Carbohydrides	42
Ethers	311
Total	4,720

SOURCE: Dube and Green (*45*).

to 15 percent), carbon dioxide (10 to 15 percent), and carbon monoxide (3 to 6 percent) as major constituents (*27, 106*). Of the more than 4,000 components identified in cigarette smoke, 400 to 500 are present in the vapor phase (*27, 45*). Table 1 lists some major classes of smoke components as recently recorded by Dube and Green (*45*). The total number of 4,720 in the table exceeds by far the total number of identified compounds because of repeated listing of the compounds that contain multifunctional groups. The acute toxicity of tobacco smoke is influenced not only by the chemical composition, aerosol concentrations, and particle sizes of the smoke, but also by the smoke pH. With a pH greater than 6.2, the smoke contains increasing amounts of unprotonated nicotine, which is the most toxic form of this habituating agent (Figure 1) (*26*). The unprotonated nicotine is at least partially present in the vapor phase and thus is likely to be more rapidly absorbed by the smoker (*5*).

The U.S. cigarette is filled with a blend of tobaccos consisting of Bright, Burley, and Turkish types. Its mainstream smoke pH lies between 5.5 and 6.1. The smoke of cigarettes and cigars made up entirely of Burley or dark tobacco varieties has pH values of about 6.5 for the first puffs and up to 8.0 for the last puffs (*26*).

Sidestream smoke, which is formed between puff drawings, is freely emitted into the air from the smoldering tobacco products. The peak temperature in the burning cone of a cigarette during puff drawing is about 900°C and between puffs it is about 600°C (*162*). This is an important factor for the divergence of specific toxic agents generated in mainstream and sidestream smoke. Another major

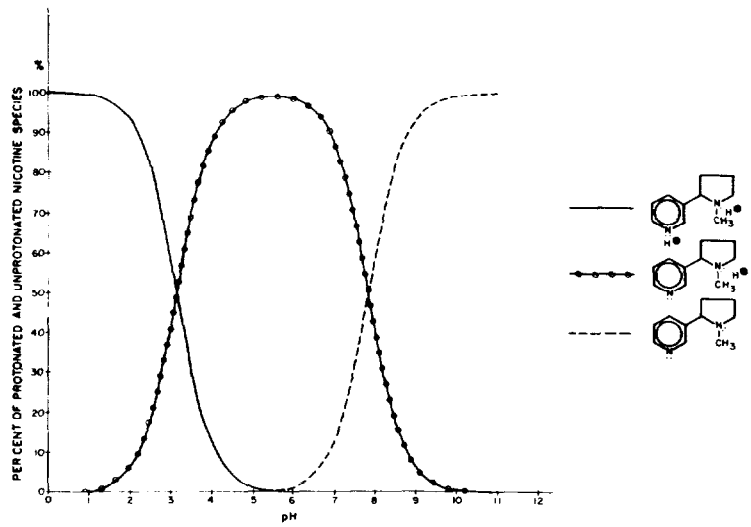


FIGURE 1.—Protonation of nicotine
SOURCE: Brunnemann and Hoffmann (*26*).

difference is that the sidestream smoke leaving the site of formation is subjected to greater air dilution and faster temperature decline than is the mainstream smoke, which travels through the tobacco column and is then inhaled as a concentrated aerosol. These conditions for sidestream smoke generation favor formation of aerosol particles of smaller size (0.01 to 0.1 μm) than those occurring in the mainstream smoke (0.1 to 1.0 μm) (*12*). The pH of sidestream smoke of a U.S. blended cigarette varies between 6.7 and 7.5, compared with pH values of less than 6.2 for the mainstream smoke of the same cigarette (*26*). This sidestream smoke thus contains free nicotine, which is essentially absent in mainstream smoke. Furthermore, during smoldering, sidestream smoke is generated in a zone that is even more oxygen deficient than the zones involved in mainstream smoke generation during puff drawing. Consequently, components that are primarily formed in a reducing atmosphere are released into the environment to a greater extent than those formed in mainstream smoke that is inhaled by the smoker. Table 2 lists the amounts of some selected toxic compounds in mainstream smoke and the ratios of undiluted sidestream smoke components to mainstream smoke components (*69*).

The air dilution of sidestream smoke emitted into the atmosphere is, of course, a determining factor for any assessment of human exposure. Nonetheless, in risk assessment, consideration must also

TABLE 2.—Distribution of selected toxic compounds in cigarette mainstream smoke (MS) and sidestream smoke (SS) of nonfilter cigarettes

Compound	MS	SS/MS
Gas phase		
Carbon monoxide	10–23 mg	2.5–4.7
Carbon dioxide	20–60 mg	8–11
Formaldehyde	70–100 μg	0.1–≃50
Acrolein	60–100 μg	8–15
Acetone	100–250 μg	2–5
Pyridine	20–40 μg	10–20
3-Vinylpyridine	15–30 μg	20–40
Hydrogen cyanide	400–500 μg	0.1–0.25
Nitrogen oxides (NO_X)	100–600 μg	4–10
Ammonia	50–130 μg	40–130
N-Nitrosodimethylamine	10–40 ng	20–100
N-Nitrosopyrrolidine	6–30 ng	6–30
Particulate phase		
Particulate matter	15–40 mg	1.3–1.9
Nicotine	1–2.3 mg	2.6–3.3
Phenol	60–120 μg	2.0–3.0
Catechol	100–280 μg	0.6–0.9
Aniline	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine	1.7 ng	30
Benz[a]anthracene	2.0–7.0 ng	2–4
Benzo[a]pyrene	20–40 ng	2.5–3.5
Quinoline	500–2,000 ng	8–11
N'-Nitrosonornicotine	200–3,000 μg	0.5–3
N-Nitrosodiethanolamine	20–70 ng	1.2
Nickel	20–80 ng	13–30
Polonium-210	0.03–0.5 pCi	?

SOURCE: Hoffmann et al. (*70*).

be given to the fact that nitrogen oxide (NO), emitted into the environment as a sidestream smoke component, is rapidly oxidized to the more toxic nitrogen dioxide (NO_2) (*27*).

Nicotine

Chemistry

A number of observations have supported the concept that nicotine is the major habituating agent in tobacco and tobacco smoke (*90*). In addition to nicotine, tobacco contains a large variety of other alkaloids, most of which are 3-pyridyl derivatives (Figure 2). In the blended U.S. cigarette, nicotine constitutes 85 to 95 percent of the total alkaloids. Its concentration in the leaf depends primarily on the tobacco type and variety, stalk position, and cultivating practices (*140*). A study on the fate of ^{14}C-labeled nicotine, added in the form of

a salt solution to the tobacco rod of a filter cigarette, revealed that 14.9 percent of labeled nicotine emerged in the mainstream smoke and 37 percent appeared in the sidestream smoke; 18.5 percent of ^{14}C-nicotine was deposited in the butt, and the remainder ($\cong$ 30 percent) was broken down into pyrolysis products (Table 3) (*73*). The major pyrolysis products of nicotine in MS and SS of cigarettes are carbon dioxide, carbon monoxide, 3-vinylpyridine, 3-methylpyridine, pyridine, myosmine, and 2,3'-dipyridyl (*130*).

In most countries, cigarettes have shown a gradual and significant reduction over the last three decades in the sales-weighted average delivery of nicotine. In the United States the sales-weighted average nicotine yields decreased from 2.7 mg in 1955 to $\geq$1.0 mg in 1982 (*146*). These nicotine reductions have been achieved primarily by technological modifications and perhaps some agricultural changes. The technological methods encompass extraction, oxidation or transformation of nicotine into less toxic compounds (*91*), formulation, and whole leaf curing. Reduction of nicotine delivery may be achieved by lowering the transfer of the alkaloid from tobacco into the smoke. This is accomplished by use of expanded tobacco laminae, adding leaf mid-veins and stems in the form of tobacco sheets (reconstituted tobacco), and by modifications of cigarette paper and by filtration (air dilution). From an agricultural standpoint, breeding lines have been developed with low levels of nicotine; however, these are not being used in commercial varieties at present (*35*).

In 1982, about 90 percent of the U.S. cigarettes sold had filter tips made of cellulose or cellulose acetate or combinations of these with charcoal. Twenty-five percent of these filter cigarettes were perforated to allow greater air dilution of the drawn smoke puffs. More recent filter construction utilizes longitudinal air channels in addition to perforation for maximal smoke dilution by air (*70, 146*).

From the machine smoking of cigarettes, using standardized parameters of taking one puff per minute of 2 seconds' duration with a volume of 35 ml, the U.S. Federal Trade Commission reported in March 1983 that the nicotine values of 208 commercial brands ranged from $<$0.05 to 2.0 mg per cigarette (*146*). However, many people who smoke these cigarettes derive very different levels of smoke components from them, primarily because nicotine delivery in the mainstream smoke influences human smoking behavior and causes many smokers of low-yield products to draw puffs more frequently, take larger puff volumes, and inhale more deeply. This phenomenon has been observed by determining the smoking profiles of individuals or by assaying nicotine and cotinine in the sera of smokers (*64, 65, 127*). Cigarette filter construction that allows partial occlusion of the perforations or air channels of the filter tip may also lead to delivery of higher concentrations of mainstream smoke (*89*). Nicotine in mainstream and sidestream smoke of tobacco products is

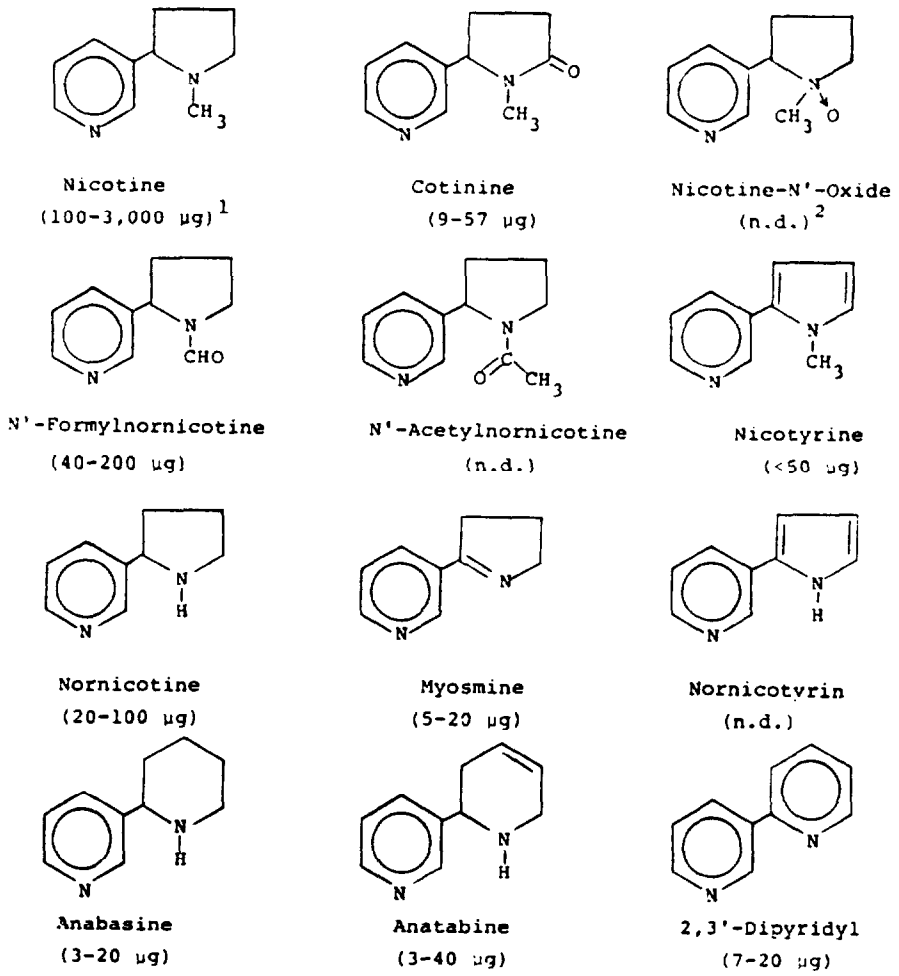


FIGURE 2.—Major alkaloids in tobacco and tobacco smoke

[1] Numbers within parentheses denote µg in the smoke of one cigarette.
[2] n.d.: Not determined.
SOURCE: Schmeltz and Hoffmann (*130*).

today primarily quantitated by gas chromatography (*151*). In physiologic fluids such as saliva, serum, or urine, smokers' exposure to nicotine is assessed by measuring the alkaloid itself or its major metabolite, either by gas chromatography with a special detector (*63*)

TABLE 3.—Distribution of nicotine and its pyrolysis products in cigarette smoke

Smoke products	Nicotine (percent)	Nicotine pyrolysis products (percent)
Mainstream particulates	14.9	0.6
Mainstream vapor phase	0.0	4.1
Sidestream particulates	37.0	4.1
Sidestream vapor phase	0.0	16.3
Butt (deposition)	18.5	1.7
Ash	0.0	0.0
Total	70.4	26.8

SOURCE: Houseman (*73*).

or, for large volumes of analyses, preferably by radioimmunoassay (RIA) (*92*).

Metabolism

The quantity of nicotine absorbed by the smoker depends on a number of factors, such as its concentration in the smoke, the individual's smoking pattern, and the smoke pH. As discussed earlier, pH values greater than 6.2 increase the amount of unprotonated nicotine in the smoke (Figure 1) (*26*). In the oral cavity, nicotine absorption varies between 4 and 45 percent (*5*). In the case of cigar smoke, the presence of free nicotine in the vapor phase, which is readily absorbed, and the harsh nature of alkaline smoke appear to be the major reasons for the cigar smoker's tendency to avoid inhalation of this smoke (*144*). That levels of cotinine in the serum of cigar smokers approximate those of cigarette smokers supports the concept that nicotine from cigar smoke is absorbed through the mucous membranes of the oral cavity. Smokers of blended cigarettes and of British types of cigarettes ($pH < 6.2$) tend to inhale the smoke. In general, between 15 and 25 percent of the nicotine in tobacco appears in cigarette mainstream smoke, from which up to 90 percent is absorbed (*162*). The extraction of nicotine from the lungs occurs quite efficiently (*143*). Nicotine enters the pulmonary capillary blood and reaches the brain via the arterial systems (*4*).

The metabolism of nicotine occurs principally in the liver. Its main metabolite, cotinine, appears in the blood within a few minutes after inhalation, and significant amounts of other metabolites appear in the tissues after about 5 minutes. The kidneys and lungs may, to a minor extent, also be involved in the metabolism of nicotine (*24, 143*).

Figure 3 illustrates the pathways of the metabolism of nicotine (*54*). Cotinine is the major metabolite of nicotine. It appears within a few minutes in the blood of smokers and has a half-life time of between 20 and 30 hours (*92*). Cotinine has been detected in

concentrations up to 10 μg per milliliter in the urine of smokers and up to 40 ng in the urine of nonsmokers who remained in a heavily polluted indoor environment for a minimum of 1 hour (*65, 69*). Nicotine-N′-oxide has been detected in the urine of smokers (*55*). In the oral cavity of man, nicotine-N′-oxide is reduced to nicotine (*78*). It has also been found that ingested nicotine-N′-oxide is reduced to nicotine by the gut flora or by intestinal enzymes (*54*). Nornicotine has been observed to be formed by N-demethylation of nicotine (*54*). γ-(3-Pyridyl)-γ-methylamino butyric acid has been identified in human urine as 3-pyridylacetic acid, the major end product of nicotine metabolism (*54*).

Association With Cardiovascular Diseases

The pharmacological effects of nicotine absorbed by inhalers might be considered small and transient, but they are repeated many times each day and act directly on the sympathetic and parasympathetic cells of the central nervous system (CNS). Nicotine exerts a direct effect on ganglion cells, producing transient excitation followed by depression or transmission blockade. At the level of the central nervous system, nicotine causes CNS stimulation followed by CNS depression (*133*).

Nicotine, like acetylcholine, discharges adrenaline from the adrenal glands and other chromaffin tissue, and releases noradrenaline from the hypothalamus. It also releases antidiuretic hormone from the pituitary (*33*), and by excitation of chemoreceptors in the carotid body, augments various reflexes (*36*).

The cardiovascular responses to nicotine, in general, parallel those that follow stimulation of the sympathicoadrenal system. Because nicotine has both stimulant and depressant effects, the responses of the cardiovascular system represent the sum of several different modes of action of this compound.

Recently, progress has been made in identifying nicotine receptor sites in the brains of animals (*81*). When microinjected into the third cerebral ventricle, nicotine increased cardiac and respiratory rates, but it did not alter these parameters when microinjected into the periaqueductal gray.

Most studies have shown that in people with known coronary heart disease, cigarette smoking increases the incidence of angina pectoris, although angina directly precipitated by smoking is rare. With additive risk factors such as hypertension, the threshold for attacks of angina can be significantly lowered by daily cigarette smoking. A long-term followup study of part of the Framingham cohort demonstrated a lack of association between smoking at diagnosis and subsequent cardiovascular events, however (*74*). This appeared to be related to changes in habits following diagnosis, implying that improved prognosis could be achieved by withdrawal

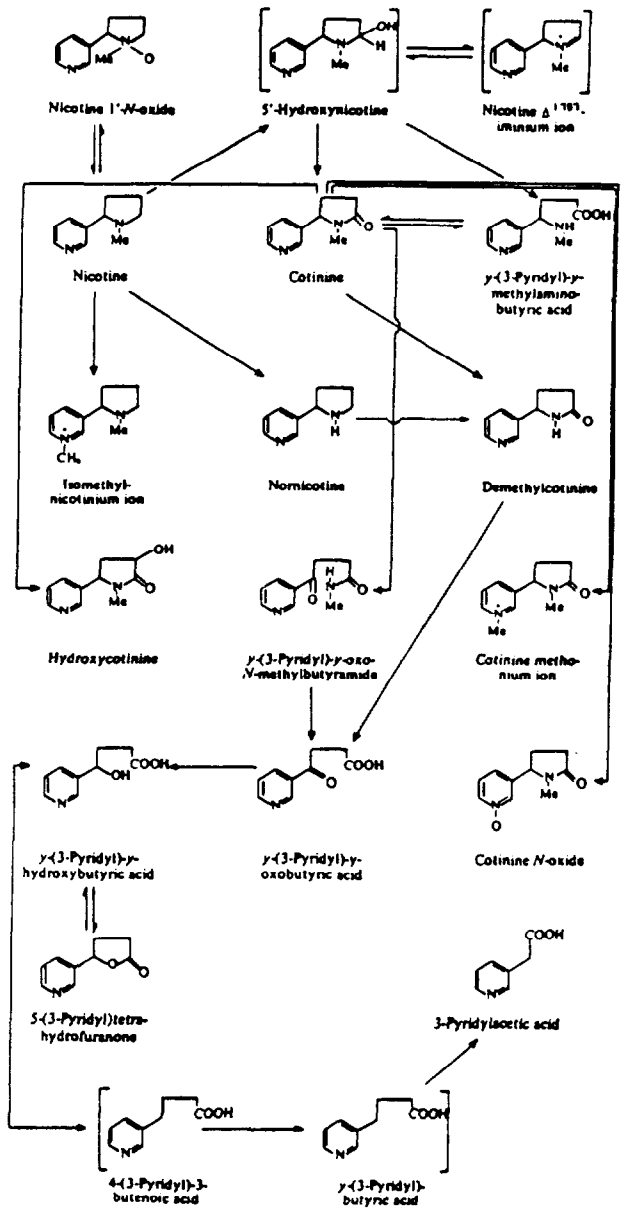


FIGURE 3.—Pathways of nicotine metabolism
SOURCE: U.S. Department of Health, Education, and Welfare (*144*).

TABLE 4.—Effects of nicotine on the cardiovascular system

Increases in blood pressure
Increases in heart rate
Electorcardiographic changes
Nonspecific ST and T-wave changes
Increased conduction velocity, propensity toward arrhythmias
Exacerbation of angina in coronary patients
Diminished left ventricular performance in coronary patients

SOURCE: Stimmel (*136*).

of daily cigarette smoking. The relationship here cannot be attributed solely to removal of nicotine; it can also be related to improvements in cardiovascular status such as increased oxygen saturation.

The exact mechanism whereby nicotine could trigger a cardiovascular event is unknown. However, a common initial feature of several suggested mechanisms is a sympathetic discharge (Table 4) (*14*). This stimulation of sympathetic nerves, with consequent release of the neurotransmitter norepinephrine within the myocardium, has been shown to lower the ventricular fibrillation threshold in animals (*38*). Responses to sympathetic activity such as hemodynamic parameters of heart rate and systolic blood pressure generally reflect plasma nicotine concentrations (*88, 112, 135*). Increase in pulse rate and systolic pressure, decrease of pressure pulse transit time, and digital blood flow are well correlated with nicotine levels of the cigarettes smoked (*88*); the same effects can be noted with intravenous injection of varying doses of L-nicotine (*150*).

In a recent study on the cardiovascular effects of infused nicotine, Benowitz and colleagues (*18*) showed that nicotine infusions could achieve plasma concentrations and cardiovascular effects similar to those induced by cigarette smoking. Heart rate increased after low concentrations of nicotine were administered and reached a plateau, beyond which increasing blood concentrations of nicotine had no effect. In these studies, as in those of Cryer et al. (*38*), elevations in pulse rate and blood pressure occurred promptly after the start of nicotine exposure and preceded the investigators' measurement of increased increments of plasma epinephrine and norepinephrine concentrations. These hemodynamic effects of nicotine are probably not mediated by circulating catecholamine levels, but are due to local release of the sympathetic neurotransmitter norepinephrine from adrenergic axon terminals.

The increase in circulating catecholamines has been demonstrated to be nicotine dose dependent by Hill and Wynder (*66*), who found an increase in epinephrine levels in plasma to be proportional to the nicotine content of the cigarette smoked. Although elevated with smoking, norepinephrine levels were not correlated with plasma

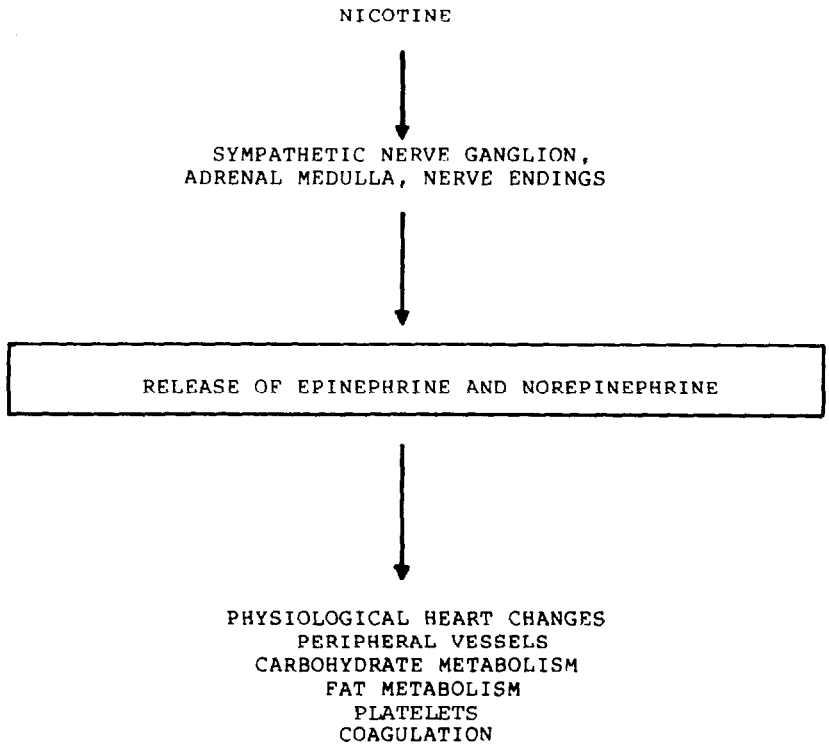


FIGURE 4.—Net results of catecholamine elevations as mediated through nicotine stimulation

SOURCE: Schievelbein and Eberhardt (*129*).

nicotine. The release of epinephrine is probably mediated through the adrenal medulla and chromaffin tissue. A more recent study showed that when the pH of the smoke is altered to favor more effective absorption of the alkaloid, smokers compensate to adjust nicotine intake, resulting in modulation of the epinephrine response (*59*).

The net results of catecholamine elevations as mediated through nicotine stimulation are summarized in Figure 4. In general, the cardiovascular responses of increased heart rate and augmented contractility create a variable oxygen need; nicotine also dilates the coronary arteries, which exerts a measurable effect only in healthy individuals without coronary heart disease (*129*).

Available evidence suggests that the release of adrenergic transmitters by nicotine and other cholinergic agonists is mediated by nicotine receptors (*159*). Norepinephrine outflow from adrenergically innervated tissues is evoked by nicotine and the nicotinic agonist dimethylphenylpiperazinium, but not by the muscarinic agonists methacholine and oxytremorine (*20*). Studies using a variety of inhibitors of nicotinic receptors have resulted in a number of possible and related mechanisms of action of nicotine on the central nervous system and the cardiovascular system: (a) prevention of inactivation of the adrenergic transmitter after its release, (b) facilitation of adrenergic transmitter release, (c) involvement of histamine (*31*), (d) mediation of nicotine by neuronal uptake, (e) induction of nerve action potentials, (f) depolarization of nerve terminals, and (g) exocytotic release of adrenergic transmitter. These mechanisms are not necessarily mutually exclusive.

Through these mechanisms, nicotine might exert powerful effects on the sympathicoadrenal control of cardiovascular function. Many issues remain to be elucidated and understood, however, such as the effects of drug interactions with nicotine (*42*), the interindividual variability in metabolism of this alkaloid (*18*), and tolerance (*132*), as well as the habituating mechanisms of the cigarette smoking habit itself (*77*).

In addition to hemodynamic perturbations, nicotine intake has been implicated in atherosclerotic changes in the arterial wall itself. Nicotine has been associated with acceleration of atherosclerotic disease, the initiation of which is becoming more clearly understood. Experimental evidence is emerging that links atherogenesis to tobacco smoke inhalation, possibly through mechanically induced intimal damage as well as through hypoxia. The pathogenesis of vascular injury might occur via two mechanisms. The first mechanism is accelerated by high levels of blood fat, particularly cholesterol in the low density lipoprotein fraction, and it is the abnormal accumulation of this lipid in the lining of large arteries that leads to changes in cells of the arterial wall, causing a thickened intima rich in fat and smooth muscle cells.

The other mechanism of atherogenesis resides in vessel injury and thrombosis, with the thrombus persisting and becoming organized, leading to vessel wall thickening (*103*). Plaque development may therefore involve damage to the intima and a complex interaction between intima and the circulating blood, resulting in (a) platelet release of mitogenic factors, (b) increased uptake of serum lipoproteins, and (c) intracellular deposition of lipid (*123*). It has been shown that platelets and cells, such as macrophages, can make available at sites of injury a protein that will cause smooth muscle cells to proliferate and another that will make them migrate into the arterial intima (*122*).

Unfortunately, we have relatively little evidence about how the endothelium can be injured. Blood flow, particularly at a high shear rate, can damage the endothelium, and high serum lipid levels can be associated with vessel injury (*125*). Immune reactions have been shown to damage vessels, and products from cigarette smoke components are suspected of causing injury to the cellular lining of vessels (*87*).

Nicotine can be implicated in the processes of atherogenesis through several of its known actions on the cardiovascular system (*47*). Via catecholamine release and the subsequent increase in free fatty acids, nicotine affects different steps in blood coagulation pathways, including platelet aggregation (*48, 129*) and increased fibrinolytic activity, with possible injurious effects to the cells lining the arterial wall. Blood pressure and heart rate can influence the blood shear rate, and transitory increases in blood sugar can influence basic metabolic rates (*42*).

A desquamating effect of nicotine on the vascular endothelium has been demonstrated in rabbits when nicotine was given in relatively low doses, as compared with those received by cigarette smoking (*23*). In a clinical assay, smoking two cigarettes increased the number of circulating endothelial cells by 50 percent. The interaction of nicotine and other cigarette smoke constituents could influence this increase in endothelial cells released into the bloodstream (*137*).

The possible role of prostaglandins in the promotion of atherogenesis is tied in with the nicotine induction of altered prostaglandin activity (*155, 157*). Evidence suggests that smoking causes a thromboxane (TxA_2):prostacyclin ($PG1_2$) imbalance. Nicotine increases platelet activity in vitro, and cigarette smoking in general has been shown to increase this activity in humans (*95*) as well as to potentiate platelet aggregability in the presence of hyperlipidemia (*67*). Nicotine inhibits the ability of coronary arteries to synthesize prostacyclin-like substances in vitro, an effect that is more pronounced in vascular cultures derived from patients who smoke than from nonsmoking control subjects (*156*). This phenomenon and alterations in endothelial barrier functions have also been investigated in umbilical arteries derived from smoking and nonsmoking mothers (*7*). Pronounced changes were seen in the endothelium of the vessels derived from smoking mothers. These consisted of swelling of the cells with numerous blebs on the luminal membrane. In addition, extensive edema of the subendothelial spaces was a regular feature, as was an increase in basement membrane thickness. These changes are consistent with an increase in endothelial permeability (*7*).

Cigarette smoking and nicotine in particular may therefore alter platelet function and prostaglandin production in potentially deleterious ways, suggesting that smoking may interfere with vascular

defense against platelet deposition, a factor in atherogenesis (*124*). Specifically, nicotine might alter the occupancy of endothelial receptors for β-adrenergic catecholamines, increasing the intracellular concentration of cyclic AMP and inhibiting the release of arachidonic acid from endothelial cell phospholipids, and thereby reducing prostacyclin synthesis (*1*).

Nicotine has been implicated at other levels of arterial cell function. This alkaloid has been found to produce an exposure-time- and concentration-dependent effect on the lysosomes of endothelial cells through increases in lysosome fragility and formation of large acid phosphatase positive vacuoles, presumably lysosomes, in rat endothelial cells (*158*). These findings suggested that the lysosomal vacuolar system should be examined as a possible target for cellular dysfunction following chronic exposure to nicotine.

Alterations in the levels of lysosomal enzymes in atherosclerotic tissue have been demonstrated in the presence of single risk factors including hypercholesterolemia (*60*), hypertension, and diabetes mellitus (*160*) in animals, as well as in diseased areas of human vessels (*49*). Inhalation experiments have shown that aortic tissue from animals chronically exposed to cigarette smoke exhibited increased levels of several lysosomal enzymes as well as cholesterol and cholesteryl esters (*57*). Studies are currently being carried out to determine the specific cigarette smoke constituents responsible for these changes.

Cigarette smoking has been implicated in elevation of serum lipids and changes in lipoprotein distribution (*117*). Reports in the literature run from no alteration (*118*) to significant changes in the direction of those levels promoting atherogenesis (*25, 71*). By stimulating sympathetic nervous activity and catecholamine release, nicotine can cause an elevation in plasma free fatty acids and increased secretion of very low density lipoprotein triglycerides (*21*). Kirchbaum and colleagues (*84*) found that the rise of free fatty acids in plasma produced by smoking was twice as high in patients who had suffered a myocardial infarction as in controls. This rise in free fatty acids is probably a result of catecholamine-mediated lipolysis and may be an important mediator in the production of endothelial cell injury (*161*). In addition, cigarette smoking in general is associated with a reduction in high density lipoprotein apoprotein components (*19*) and may attenuate this lipoprotein's antiatherogenic properties by altering surface phospholipid constituents (*62*).

Carbon Monoxide

Chemistry

The formation of carbon monoxide (CO) occurs in and close to the burning cone of a cigarette by thermal decomposition, by reaction of

tobacco with atmospheric oxygen, and by secondary reactions of tobacco with carbon dioxide, water, and other primary pyrolysis products (*13, 69*). Studies with labeled precursors have shown that CO is formed at temperatures above 460°C and that about 30 percent of it derives from thermal decomposition of tobacco, 36 percent from combustion of tobacco, and 23 percent from reduction of carbon dioxide (*13*). The yield of CO in the mainstream smoke of a cigarette depends on the amount of tobacco and the type of paper burned during puff drawing, the concentration of pyrolytic precursors, the temperature profile of the tobacco during puff drawing, and the permeability of the wrapper for the outward diffusion of CO (*111*). The CO concentration in the inhaled smoke is also a function of the permeability of the cigarette paper and of the physical and chemical properties of the filter (*86, 153*).

The importance of the air velocity created during puff drawing is demonstrated by the significant increase in the smoke with increasing puff volume (Figure 5) (*69*). The somewhat higher CO yields in the smoke of cigarettes with conventional filter tips compared with those from nonfilter cigarettes have been attributed to the loss of air dilution and to the increased smoke velocity that occurs when the last 15 to 25 mm of the tobacco column are replaced by a filter tip with a nonporous wrapper (*69, 153*). This concept is also reflected in the higher CO yield for a filter cigarette smoked with puffs of different volumes (Figure 5).

In recent years, cigarettes with perforated filter tips have gained in market share. The air entering through the perforations in these filter tips dilutes the mainstream smoke and thus reduces the concentration of CO in the smoke (Figure 5). In addition, carbon monoxide is selectively reduced, most likely because of the reduced velocity of air entering the burning cone (*86*). Finally, the newly introduced filter cigarettes with longitudinal air channels reduce CO in the smoke even further (*68*). However, as discussed before, because of the compensatory changes in smoking behavior that smokers make in order to satisfy their need for a certain amount of nicotine and because of the possible obstruction of perforated filter tips or their air channels during puff drawing, the smokers may not fully benefit from the intended air dilution of the smoke (*64, 65, 68, 89, 127*).

Association With Cardiovascular Diseases

The health effects of exposure to carbon monoxide are not fully known. However, research findings in selected population groups indicate that carbon monoxide acts as an added stress factor to precipitate cardiac symptomatology or ischemic episodes in individuals already compromised by coronary disease (*3*). Additionally, excessive levels of carbon monoxide in the blood have been found by

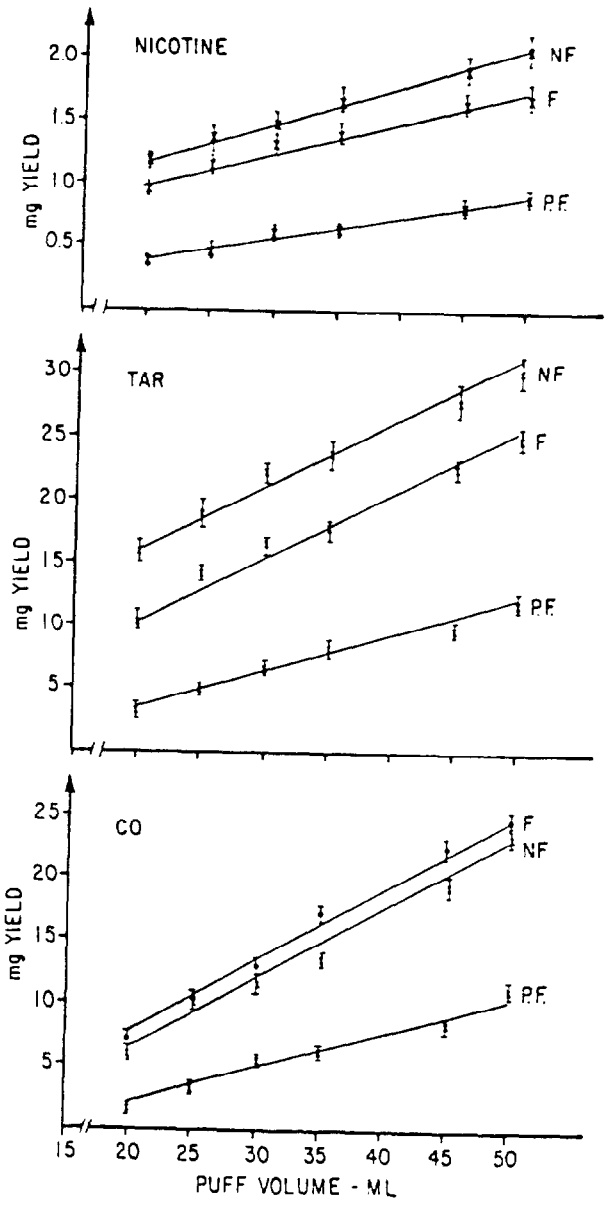


FIGURE 5.—Carbon monoxide, tar, and nicotine in the smoke of cigarettes

NOTE: NF = Nonfilter; F = Filter; PF = Perforated Filter.
SOURCE: Hoffmann et al. (69).

some investigators to impair certain perceptual and motor functions (*104*).

Carbon monoxide is a common industrial pollutant generated by any burning process. It is odorless and tasteless and gives no warning of its presence in most circumstances, thus allowing for chronic exposure over extended periods of time. The early symptoms of carbon monoxide poisoning often resemble those of a variety of diseases; thus, tissue hypoxia might occur in healthy people without forewarning (*163*).

Carbon monoxide combines with hemoglobin in large quantities. Its chemical affinity for hemoglobin is over 200 times greater than that of oxygen. The ability of carbon monoxide to cause tissue hypoxia stems from two effects on circulating processes: (a) a reduction in the total amount of oxygen carried by red cells in blood, which reduces delivery of oxygen to tissues, and (b) a shift to the left of the oxyhemoglobin dissociation curve of the blood that contains both oxyhemoglobin and carboxyhemoglobin. The leftward shift of the oxyhemoglobin dissociation curve decreases the tension at which oxygen molecules are dissociated from hemoglobin, and therefore decreases the driving pressure for diffusion of oxygen into tissues and cells (*142*). The concentration of carboxyhemoglobin reached in blood will depend upon the concentration of carbon monoxide in the inhaled gas mixture as well as on the alveolar concentration, and on arterial oxygen tension, duration of exposure, and ventilation volume (*142*).

It is noteworthy that carbon monoxide binds to muscle myoglobin as well as to hemoglobin and may exert tissue hypoxia by interfering with oxygen transport to muscle mitochondria. It can also have an effect on other hemoproteins such as those present in the cytochrome oxidase system (*35*). Cytochrome P-450, a mixed-function oxidase, probably does not bind sufficient carbon monoxide to cause inhibition of drug hydroxylation, even at a carboxyhemoglobin saturation of 15 to 20 percent (*126*). However, smokers and nonsmokers differ in their clinical reactivity to drugs such as phenacetin and diazapam through acceleration of biotransformation processes. This increased drug metabolism is believed to result from an induction of microsomal drug-metabolizing enzymes after chronic exposure to tobacco smoke (*148*). Although smoking in general results in accelerated enzyme induction, carbon monoxide has been implicated in decreased hepatic protein synthesis, a phenomenon that can be duplicated by chronic cigarette smoke exposure (*52*). This effect could be due to a deleterious reaction of hepatic tissue because of binding of carbon monoxide to intracellular hemoproteins.

It is possible that carbon monoxide may bind to hemoproteins other than cytochrome oxidase, hemoglobin, or myoglobin in sufficient amounts to inhibit their function. Tryptophan dioxygenase and

catalase have high affinities for carbon monoxide, which in the first case, could result in increased serotonin levels in several tissues, and through the latter enzyme, could cause the cellular accumulation of hydrogen peroxide, a toxic oxidant (*126*).

Cigarette smoking causes increased carboxyhemoglobin levels, thereby reducing the oxygen-carrying capacity of the blood and subsequent tissue oxygenation and, possibly, cellular metabolism. Interpretation of the effects of carbon monoxide absorption by healthy people is a subject of much controversy because effective threshold levels have not been established. Environmental exposure to carbon monoxide may be without chronic consequences in healthy people who appear able to compensate for any acute effects at levels of industrial exposure. However, in patients with angina pectoris, exposure to carbon monoxide has reduced exercise time until the onset of chest pain (*3*).

Atherosclerosis is a multifactorial disorder in which cigarette smoking and carboxyhemoglobin levels may exert varying effects, depending upon the other risk factors present. Carbon monoxide is believed to be a contributing factor to the acceleration of the disease process. Wald and associates (*152, 153*) have suggested that carboxyhemoglobin levels in tobacco smokers correlate better than a smoking history with the development of myocardial infarction, angina pectoris, and intermittent claudication. However, it should be pointed out that in such studies, elevation in carboxyhemoglobin also reflects the absorption of other constituents of tobacco smoke.

In his earlier studies, Astrup (*8*) found that carbon monoxide or decreased oxygen tension enhanced coronary atherosclerosis in cholesterol-fed rabbits and suggested that high carboxyhemoglobin levels resulting from tobacco smoking were associated with the development of occlusive arterial vascular disease. More recent experiments, conducted in a blind fashion, confirmed the presence of myocardial lesions, but failed to produce aortic atherosclerosis (*9*), although other researchers had noted morphological alterations in coronary arteries similar to those seen in the earlier experiments (*8, 40*).

Animal experiments on accelerated atherogenesis with carbon monoxide must be considered to be unsatisfactory, and although clinical trials have linked elevated carboxyhemoglobin levels with cardiovascular symptomatology, a cause and effect phenomenon for carbon monoxide and disease of the arterial wall has not been elucidated.

Carbon monoxide exposure has been related to increases in circulating blood lipids. This was first demonstrated in rabbits in which carboxyhemoglobin levels were 15 to 25 percent, resulting in elevations of serum cholesterol for a transient 2 to 3 weeks following exposure (*10*). In an epidemiological study by Van Houte and

Kesteloot (*147*) involving 42,000 subjects, significantly higher serum cholesterol levels were demonstrated in male smokers than in nonsmokers, particularly in the 30- to 39-year age group. The early Framingham results also reported slightly higher serum cholesterol levels among smokers (*41*), whereas Blackburn et al. (*22*) report nonsignificant differences between smokers and nonsmokers. Many other epidemiological investigations have analyzed the correlation between smoking status, serum cholesterol levels, and lipoprotein distributions, but the majority of results suggest a trend rather than significance in support of a connection between smoking and elevated cholesterol (*100*). This relationship does not offer an explanation for an effect of cigarette smoking on serum lipid levels, but experimental evidence suggests that carbon monoxide might exert an effect on the metabolism of chylomicron remnants (*51*). Ascorbic acid levels could limit the conversion of cholesterol to bile acids (*85*), or carbon monoxide could diminish hepatic degradation of lipoprotein constituents (*40*).

Carbon monoxide has also been implicated in the noted decrease in patency following vascular surgery and arterial reconstruction among continuing cigarette smokers (*138*). Cigarette smoking as measured by extrapolation from carboxyhemoglobin values had a definite adverse effect on the healing process and success rate of vascular surgery (*20, 56*).

Additional Contributors

Hydrogen Cyanide

Nitrates in tobacco serve as precursors for hydrogen cyanide (HCN) in the smoke (*61, 79*). This concept has been supported by studies in which ^{15}N-labeled nitrates of potassium, sodium, or calcium, respectively, had been added to cigarette tobacco and in which the isolated HCN from the smoke was found to contain ^{15}N-HCN (*79*). However, tobacco proteins appear to be the major group of precursors for HCN in the smoke (*27, 80*). This was demonstrated in pyrolysis studies with tobacco protein and amino acids and by recovery in the smoke of ^{15}N-HCN from cigarettes spiked with ^{15}N-glycine (*27, 80*). It has been shown that HCN is formed via N-heterocyclic intermediates and from pyrolidine, the decarboxylation product of proline (*80*). From these intermediates, hydrogen cyanide is split off in the pyrolysis-distillation zone of the burning cigarette under the opening of the N-containing ring (*27, 80*).

Several methods have been explored for the selective reduction of hydrogen cyanide in cigarette smoke. Charcoal-containing filter tips can remove 70 to 80 percent of the HCN from cigarette mainstream smoke (*139*). With increasing smoke dilution through filter perforation, HCN can be selectively reduced up to 80 percent, with a 70

percent ventilation rate (*105*). The extraction of protein fractions from cigarette tobacco leads also to a selective reduction of HCN (*141*). The smoke of one cigarette contains from 20 to 480 μg of HCN, the lowest values being measured in the smoke of cigarettes with charcoal-containing filter tips (*120*).

Although only nicotine and carbon monoxide have been incriminated as contributors to the increased risk of cigarette smokers for cardiovascular disease, other gas phase constituents might also play roles in the pathogenic processes. Hydrogen cyanide is an inhibitor of several respiratory enzymes and as such can influence cellular metabolism in the myocardium and arterial wall. It is also a powerful ciliatoxic agent allowing for decreased efficiency in removal of tar constitutents from the respiratory system (*16*).

The arterial effects of hydrogen cyanide, nitric oxide, and carbonyl sulfide were investigated by Hugod and Astrup (*76*) in experiments in which rabbits were exposed to these compounds alone or in combination with carbon monoxide. The duration of exposure was from 5 days to 12 weeks, and aortas were assessed morphologically for intimal damage suggestive of early atherosclerotic changes. No histotoxic effect on intimal or subintimal morphology was noted, and a parallel experiment demonstrated no effect on the coronary arteries (*75*). The duration of exposure to these compounds must be considered short, however, with the possibility that prolonged exposure might result in morphological or enzymatic alterations.

Nitrogen Oxides

A number of studies have shown that nitrate is a major precursor for nitric oxide (NO) and traces of nitrous oxide (N_2O) and nitrogen dioxide (NO_2) found in cigarette mainstream and sidestream smoke (*79, 134*). The mainstream smoke of a cigarette contains from 6 to 600 μg of NO per cigarette, depending primarily on the nitrate content of the tobacco blend and the nature of the filter tip (*105*). The correlation of nitrate content of tobacco with nitric oxide yield in the mainstream smoke appears to be linear (*27*). The smoke of cigarettes made with Burley tobacco and particularly those made with Burley stems, which are rich in nitrate, is especially high in nitric oxide (*29, 107*). Tobacco proteins appear also to contribute to the NO yield in cigarette smoke (*79*).

The concentration of nitrogen dioxide and that of methyl nitrite in freshly generated cigarette smoke is very minute (<5 μg/cigarette); however, these agents increase rapidly as a function of the aging of mainstream and sidestream smoke. Within about 3 minutes, 50 percent of NO is oxidized to NO_2 (*149*). The best approaches toward reducing NO in cigarette smoke are by reduction of nitrate in tobacco and by dilution of smoke by air entering through the holes of perforated filter tips (*27, 105*).

Changes in cardiac function of rats acutely exposed to nitrogen dioxide were examined by electrocardiographic records. Bradycardia and arrhythmias were observed following exposure to 20 ppm for 3 hours (*76*). These alterations were attributed to changes in parasympathetic nervous activity following exposure. The levels used were high relative to those obtained from unaged tobacco smoke. In addition, it has been suggested that enzyme-inhibiting effects associated with cigarette smoking are due to nicotine N-oxide and nitrogen dioxide. Because thiols are readily oxidized to disulfides by either nitric oxide or nitrogen dioxide, they are potent inhibitors of thiol-dependent enzymes (*116*). In the presence of cigarette smoke, scavenger cells such as macrophages may not be readily activated. In the respiratory system, the major histological sites of damage by nitrogen dioxide are the terminal and respiratory bronchioles and the proximal portions of the alveolar ducts. Nitrogen oxides are also suspected of contributing to the development of pulmonary emphysema (*43*) and the acceleration of platelet aggregation (*101*).

Carbon Disulfide

Epidemiological studies have incriminated carbon disulfide (CS_2) as a factor for the increased risk of arteriosclerotic diseases in workers in the viscose-rayon industry (*39*). The reported acute dose levels of CS_2 during workers' exposure were 20 ppm and higher (*39*). In cigarette mainstream smoke, carbon disulfide can amount to as much as 4 μg per cigarette (*72, 114*). It appears that the sulfur-containing amino acids and proteins and certain pesticides serve as major precursors for CS_2 in tobacco smoke (*15, 72*).

Cadmium

The soil supplies tobacco with traces of cadmium (Cd), which are selectively retained by the plant. Depending on the soil, the Cd in the leaf can amount to a few parts per million (*50*). The mainstream smoke of a blended U.S. cigarette may contain up to 0.2 μg Cd (*97, 102*). In the blood of cigarette smokers, Manthey et al. (*99*) found 2.47 $\pm$ 1.72 μg per liter; Cd levels in the blood of nonsmokers were only 0.43 $\pm$ 0.22 μg per liter. Cd appears to accumulate in the kidney, and has been found in higher concentrations in the kidneys of cigarette smokers than of nonsmokers (*115*).

The potential consequences of increased lifetime exposure to low levels of cadmium are not known. However, autopsy studies have revealed increased cadmium levels in persons with emphysema and hypertension (*131*). Cigarette smoke is known to contain traces of cadmium (0.1 to 0.2 μg per cigarette) (*97, 102*). It is chiefly accumulated in the liver and kidneys, and has been found in levels about twice as high in the kidneys of hypertensive cigarette smokers compared with nonsmokers in the normotensive range (*113*). It is

possible that an increased body burden of cadmium may be related more directly to blood pressure (*108*), although animal studies have implicated genetic differences in susceptibility to cadmium-induced hypertension (*109, 110*). Furthermore, epidemiological studies may be confounded by failure to separate cigarette smokers from drinkers of soft water in determining risk of elevated blood pressure from cadmium intake (*17*).

Cadmium has also been implicated in accelerated atherogenesis and altered lipoprotein patterns in White Carneau pigeons, a species often used to investigate risk factors for arterial disease (*119*). The results of these studies showed that the number and size of atherosclerotic plaques were increased in pigeons given drinking water containing cadmium or lead and that the lipoprotein profile was altered in an independent fashion. The possible mode of action of cadmium on atherogenesis is unknown, but endothelial damage is suggested by the work of Rohrer and colleagues (*121*). In their studies, pregnant rats received a single administration of cadmium (0.5 to 2.0 mg/kg), and vacuoles were observed in the endothelial cells of fetal brains. These vacuoles distorted the shape and orientation of the endothelial cells in the caudate nucleus.

Data on the relation between cigarette smoking and cadmium intake remain inconclusive. Drinking water and genetic factors may overwhelm the effects of cadmium as a cigarette smoke constituent on cardiovascular disease, and more work in this area is necessary before a cause and effect assignment can be made.

Zinc

The average zinc (Zn) content in commercial cigarettes varies between 50 and 80 ppm (*140*) and in the mainstream smoke of U.S. cigarettes between 0.05 and 0.4 μg (*102*). So far, Zn has been determined only in the urine of cigarette smokers, where it occurs in significantly higher concentration than it does in the urine of nonsmokers (*46*). Zinc is a metal component of many important enzyme systems; its availability controls the rate of synthesis of nucleic acids and protein (*98*). In fact, zinc deficiency has been associated with poor growth (*30*), and depressed plasma zinc levels have been used as indicators of myocardial infarction (*94*). In general, low zinc levels have been found to be associated with depressed health status, and supplemental zinc has not been correlated with increased risk of disease development.

Tar

The total particulate matter (TPM) of a cigarette, often referred to as tar, is defined as that portion of the smoke that is retained by a glass fiber filter. This definition is widely accepted and can be regarded as a quantitative approach, since the Cambridge glass fiber

filter retains 99.9 percent of particles of the mainstream smoke that have diameters of ≥ 0.2 μ (*154*). Different methods of smoking cigarettes and of determining tar in the smoke have been applied throughout the world; this needs to be considered when comparing data on cigarette smoke yields in various countries (*28*).

According to the U.S. Federal Trade Commission report of March 1983, the tar yields of commercial U.S. cigarettes vary from <0.5 to 30 mg (*146*). All cigarettes with >20 mg tar yield are nonfilter cigarettes, and practically all cigarettes with tar yields <12 mg are cigarettes with perforated filter tips (*146*). As discussed before, it has to be realized that the standard machine smoking method developed for a comparison of the smoke yields of commercial cigarettes does not reflect the average smoking habits of cigarette smokers, especially of those who smoke low-nicotine cigarettes (*64, 65, 89, 127*). A person's smoking habit is largely dependent on the smoker's need for nicotine. Consumers of low-nicotine cigarettes take larger puff volumes and inhale more frequently than do the smokers of cigarettes with high nicotine yields (>1.0 mg cigarettes) (*64*). At present, the most reliable assay for determining the uptake of particulate matter by an individual smoker is seen in the analysis of nicotine and cotinine in his or her serum (*58*).

In theory, reduction of the toxic components in cigarette smoke should reduce the risk for neoplasms and cardiovascular diseases. Therefore, the introduction of filter cigarettes, which should preclude the inhalation of some of the tobacco tar constituents, would be expected to reduce the incidence of respiratory and cardiovascular dysfunctions. End point analysis of the long-term followup of the Framingham cohort made it possible to test the hypothesis that those who smoke filter cigarettes would be less likely to manifest clinical symptoms of cardivascular disease than would those who smoke nonfilter cigarettes. Despite what seemed a more favorable smoking history, the filter cigarette smokers did not have lower incidence rates of cardiovascular diseases than the nonfilter smokers. This finding was unchanged after multivariate logistic regression analysis to adjust for age, systolic blood pressure, and serum cholesterol (*32*). The relationship of this seemingly negative finding to the tar component of tobacco smoke must remain imprecise because other smoke constituents covary with the tar fraction.

Respiratory complications and immune hypersensitivity have been correlated with intake of particulate phase components of tobacco smoke. Cigarette smokers exhibit greatly increased risks for pulmonary diseases, including emphysema and chronic obstructive lung disease (*144*). Such diseases can also place increased stress on the cardiovascular system. Cigarette smokers demonstrate more frequent macroscopic and microscopic lung abnormalities than do

nonsmokers, with a dose–response relationship being apparent in regard to these changes and the self-reported intensity of smoking.

Research Needs and Priorities

The evidence linking cigarette smoking to cardiovascular diseases is strong. Understanding of the mechanisms whereby cigarette smoking initiates or accelerates disease processes remains imprecise because a variety of smoke constituents exert multiple effects upon body systems.

Epidemiologic studies have correlated increases in atherosclerotic CVD death rates with increased use of cigarettes and also have shown that those persons who stop smoking do in fact exhibit lower death rates than those who continue to smoke. Despite the demonstrated association of smoking with enhanced atherogenesis, risk of coronary death in persons who stop smoking appears to revert to lower levels in a relatively short period following cessation. It is quite likely that the precipitating events leading to thrombus formation and occlusion are decreased, although fibrous plaques will not regress so rapidly (*82*).

Methods for cessation of cigarette smoking, especially among high risk populations, must be a priority in the research endeavor to reduce cardiovascular disease morbidity and mortality. Although termination of the habit is the ideal goal, it must be recognized that this is a difficult task for a number of smokers.

Reduction of the harmful components delivered to the smoker has been another priority objective, aimed at those smokers who will not give up the habit. This task has resulted in the introduction of a variety of low- and ultra-low-yield cigarettes. Whether risks for cardiovascular diseases are truly reduced when these products are used remains to be demonstrated. Several recent studies have shown that smokers alter their smoking behavior when they switch to low-yield cigarettes and can receive increased smoke constituents as they attempt to satisfy a nicotine demand (*64, 65*). This compensatory behavior may lead to accelerated atherogenesis through increased uptake of smoke constituents such as carbon monoxide, hydrogen cyanide, and nitrous oxides. Recently it was reported that the risk of a nonfatal first myocardial infarction in young men was not related to the nicotine or carbon monoxide levels of the cigarette. This could be due to compensatory behavior (*83*).

One should not ignore the proportion of the population that continues to smoke, nor should one accept unchallenged the concept of a "safe" cigarette. The main objective is to reduce the harmful constituents present in tobacco smoke. It is probable that promotion of ultra-low-yield products will not suffice, since compensatory

mechanisms may be triggered by sensory needs for taste as well as for nicotine.

A cigarette considered less harmful for cancer etiology might not reduce the risk for coronary disease. It appears to be a formidable task to develop a product that satisfies the smoker and does not increase disease risk through exposure to carbon monoxide, hydrogen cyanide, nitrous oxide, or still unknown agents.

Of the major cardiovascular risk factors, cigarette smoking is a powerful, prevalent, and potentially correctable contributor that deserves the highest priority among preventive measures to control cardiovascular disease (*82*).

Conclusions

1. Over 4,000 different compounds have been identified in tobacco smoke.
2. Nicotine exerts an effect on ganglionic cells, producing transient excitation. The pharmacological effects are small, but are reinforced several times daily in habitual smokers. The exact mechanisms whereby nicotine might influence cardiovascular events are unknown, but a lowering of the ventricular fibrillation threshold is dose related to nicotine levels.
3. Carbon monoxide may act to precipitate cardiac symptomatology or ischemic episodes in individuals already compromised by coronary disease. In addition, carbon monoxide binds to hemoproteins, potentially inhibiting their functions.
4. Several studies have shown that smokers may alter their smoking behavior when they switch to low-yield cigarettes. This compensatory behavior may lead to the increased uptake of gas phase constituents including carbon monoxide, hydrogen cyanide, and nitrous oxides.
5. It is unlikely that a "safe cigarette" can be developed that will reduce cardiovascular risk.

References

(1) ADLER, B., GIMBRONE, M.A., Jr., SCHAFER, A.I., HANDIN, R.I. Prostacyclin and β-adrenergic catecholamines inhibit arachidonate release and PGI_2 synthesis by vascular endothelium. *Blood* 58(3): 514–517, September 1981.

(2) AMERICAN CANCER SOCIETY. U.S. tar/nicotine levels dropping. *World Smoking and Health* 6(2): 47, Summer 1981.

(3) ANDERSON, E.W., ANDELMAN, R.J., STRAUCH, J.M., FORTUIN, N.J., KNELSON, J.H. Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. *Annals of Internal Medicine* 79(1): 46–50, July 1973.

(4) ARMITAGE, A.K., DOLLERY, C.T., GEORGE, C.F., HOUSEMAN, T.H., LEWIS, P.J., TURNER, D.M. Absorption and metabolism of nicotine from cigarettes. *British Medical Journal* 4(5992): 313–316, November 8, 1975.

(5) ARMITAGE, A.K., TURNER, D.M. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. *Nature* 226(5252): 1231–1232, June 27, 1970.

(6) ASMUSSEN, I. Ultrastructure of the villi and fetal capillaries in placentas from smoking and nonsmoking mothers. *British Journal of Obstetrics and Gynaecology* 87(3): 239–245, March 1980.

(7) ASMUSSEN, I. Ultrastructure of human umbilical arteries. Studies on arteries from newborn children delivered by nonsmoking, white group D, diabetic mothers. *Circulation Research* 47(4): 620–626, October 1980.

(8) ASTRUP, P. Carbon monoxide, smoking, and cardiovascular disease. *Circulation* 48(6): 1167–1168, December 1973.

(9) ASTRUP, P., KJELDSEN, K. Model studies linking carbon monoxide and/or nicotine to arteriosclerosis and cardiovascular disease. *Preventive Medicine* 8(3): 295–302, May 1979.

(10) ASTRUP, P., KJELDSEN, K., WANSTRUP, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. *Journal of Atherosclerosis Research* 7(3): 343–354, May-June 1967.

(11) BAKER, R.R. Mechanisms of smoke formation and delivery. *Recent Advances in Tobacco Science.* The 34th Tobacco Chemists' Research Conference, Richmond, Virginia, October 27, 1980. Volume 6, pp. 184–224.

(12) BAKER, R.R. Variation of sidestream gas formation during the smoking cycle. *Beiträge zur Tabakforschung* 11(4): 181–193, August 1982.

(13) BAKER, R.R. Formation of carbon oxides during tobacco combustion. Pyrolysis studies in the presence of isotopic gases to elucidate reaction sequence. *Journal of Analytical and Applied Pyrolysis* 4(4): 297–334, March 1983.

(14) BALL, K., TURNER, R. Smoking and the heart: The basis for action. *Lancet* 2(7884): 822–826, October 5, 1974.

(15) BARKEMEYER, H., BOROWSKI, H., SCHROEDER, R., SEEHOFER, F. Zur Applikation und Analytik der Dithiocarbamate. [Application and analysis of dithiocarbamate.] *Beiträge zur Tabakforschung* 1(10): 385–399, December 1962.

(16) BATTISTA, S.P. Cilia toxic components of cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker.* Volume I. Proceedings of the Third World Conference on Smoking and Health, New York City, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 517–534.

(17) BEEVERS, D.G., CRUICKSHANK, J.K., YEOMAN, W.B., CARTER, G.F., GOLDBERG, A., MOORE, M.R. Blood-lead and cadmium in human hypertension. *Journal of Environmental Pathology and Toxicology* 4(2–3): 251–260, September 1980.

(18) BENOWITZ, N.L., JACOB, P., III., JONES, R.T., ROSENBERG, J. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *Journal of Pharmacology and Experimental Therapeutics* 221(2): 368–372, 1982.

(19) BERG, K., BORRESEN, A.-L., DAHLEN, G. Effect of smoking on serum levels of HDL apoproteins. *Atherosclerosis* 34(3): 339–343, November 1979.

(20) BEVAN, J.A., SU, C. The sympathetic mechanism in the isolated pulmonary artery of the rabbit. *British Journal of Pharmacology and Chemotherapy* 22: 176–182, February 1964.

(21) BIZZI, A., TACCONI, M.T., MEDEA, A., GARATTINI, S. Some aspects of the effect of nicotine on plasma FFA and tissue triglycerides. *Pharmacology* 7(4): 216–224, 1972.

(22) BLACKBURN, H., BROZEK, J., TAYLOR, H.L., KEYS, A. Comparison of cardiovascular and related characteristics in habitual smokers and nonsmokers. *Annals of the New York Academy of Sciences* 90(1): 277–289, 1960.

(23) BOOYSE, F.M., OSIKOWICZ, G., QUARFOOT, A.J. Effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. *American Journal of Pathology* 102(2): 229–238, February 1981.

(24) BOYLAND, E., deKOCK, D.H. Nicotine metabolism. *British Empire Cancer Campaign for Research, Forty-Fourth Annual Report* Part II: 5–6, 1981.

(25) BOYLE, E., Jr., MORALES, I.B., NICHAMAN, M.Z., TALBERT, C.R., Jr., WATKINS, R.S. Serum beta lipoproteins and cholesterol in adult men. Relationships to smoking, age, and body weight. *Geriatrics* 23(12): 102–111, December 1968.

(26) BRUNNEMANN, K.D., HOFFMANN, D. The pH of tobacco smoke. *Food and Cosmetics Toxicology* 12(1): 115–124, February 1974.

(27) BRUNNEMANN, K.D., HOFFMANN, D. Pyrolytic origins of major gas phase constituents of cigarette smoke. *Recent Advances in Tobacco Science* 8: 103–140, 1982.

(28) BRUNNEMANN, K.D., HOFFMANN, D., WYNDER, E.L., GORI, G.B. Chemical studies on tobacco smoke. XXXVII. Determination of tar, nicotine and carbon monoxide in cigarette smoke. A comparison of international smoking conditions. In: Wynder, E.L., Hoffmann, D., Gori. G.B. (Editors). *Modifying the Risk for the Smoker.* Volume I. Proceedings of the Third World Conference on Smoking and Health, New York City, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 441–449.

(29) BRUNNEMAN, K.D., MASARYK, J., HOFFMANN, D. The role of tobacco-stems in the formation of N-nitrosamines in tobacco and cigarette mainstream and sidestream smoke. *Journal of Agricultural and Food Chemistry,* in press.

(30) BURCH, R.E., WILLIAMS, R.V., HAHN, H.K.J., JETTON, M.M., SULLIVAN, J.F. Serum and tissue enzyme activity and trace-element content in response to zinc deficiency in the pig. *Clinical Chemistry* 21(4): 568–577, 1975.

(31) BURROWS, M.E., VANHOUTTE, P.M. Pharmacology of arterioles: Some aspects of variability in response to norepinephrine, histamine, and 5-hydroxytryptamine. *Journal of Cardiovascular Pharmacology* 3(6): 1370–1380, 1981.

(32) CASTELLI, W.P., DAWBER, T.R., FEINLEIB, M., GARRISON, R.J., McNAMARA, P.M., KANNEL, W.B. The filter cigarette and coronary heart disease: The Framingham study. *Lancet* 2(8238): 109-113, July 18, 1981.

(33) CASTRO DE SOUZA, E.M., SILVA, M.R.E., Jr. The release of vasopressin by nicotine: Further studies on its site of action. *Journal of Physiology* 265(2): 297-311, February 1977.

(34) CHAPLIN, J.F. Breeding for varying levels of nicotine in tobacco. In: *Recent Advances in the Chemical Composition of Tobacco and Tobacco Smoke.* Proceedings of the American Chemical Society Symposium, the 173d American Chemical Society meeting, Agricultural and Food Chemistry Division, New Orleans, Louisiana, March 20–25, 1977, pp. 328–339.

(35) COBURN, R.F. Mechanisms of carbon monoxide toxicity. *Preventive Medicine* 8(3): 310-322, May 1979.

(36) COHEN, A.J., ROE, F.J.C. *Monograph on the Pharmacology and Toxicology of Nicotine.* Tobacco Advisory Council Occasional Paper 4, London, 1981, 45 pp.

(37) CORONARY DRUG PROJECT RESEARCH GROUP. Factors influencing long-term prognosis after recovery from myocardial infarction—Three-year findings of the Coronary Drug Project. *Journal of Chronic Diseases* 27(6): 267–285, August 1974.

(38) CRYER, P.E., HAYMOND, M.W., SANTIAGO, J.V., SHAH, S.D. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *New England Journal of Medicine* 295(11): 573–577, September 9, 1976.

(39) DAVIDSON, M., FEINLEIB, M. Carbon disulfide poisoning. A review. *American Heart Journal* 83(1): 100-114, January 1972.

(40) DAVIES, R.F., TOPPING, D.L., TURNER, D.M. The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. *Atherosclerosis* 24(3): 527–536, September 1976.

(41) DAWBER, T.R., KANNEL, W.B., REVOTSKIE, N., STOKES, J., KAGAN, A., GORDON, T. Some factors associated with the development of coronary heart disease. Six years' follow-up experience in the Framingham study. *American Journal of Public Health* 49(10): 1349–1356, October 1959.

(42) DAWSON, G.W., VESTAL, R.E. Smoking and drug metabolism. *Pharmacology and Therapeutics* 15(2): 207–221, 1981.

(43) DIAMOND, L. Pulmonary toxicity of nitrogen oxides. In: Gori, G.B., Bock, F.G. (Editors). *Banbury Report 3—A Safe Cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 67–74.

(44) DOYLE, J.T. Risk factors in arteriosclerosis and cardiovascular disease with special emphasis on cigarette smoking. *Preventive Medicine* 8(3): 264–270, May 1979.

(45) DUBE, M., GREEN, C.R. Methods of collection of smoke for analytical purposes. *Recent Advances in Tobacco Science* 8: 42–102, 1982.

(46) ELINDER, C.-G., KJELLSTROM, T., LINNMAN, L., PERSHAGEN, G. Urinary excretion of cadmium and zinc among persons from Sweden. *Environmental Research* 15(3): 473–484, June 1978.

(47) FISHER, E.R., ROTHSTEIN, R., WHOLEY, M.H., NELSON, R. Influence of nicotine on experimental atherosclerosis and its determinants. *Archives of Pathology* 96(5): 298–304, November 1973.

(48) FOLTS, J.D., BONEBRAKE, F.C. The effects of cigarette smoke and nicotine on platelet thrombus formation in stenosed dog coronary arteries: Inhibition with phentolamine. *Circulation* 65(3): 465–470, March 1982.

(49) FOWLER, S., BERBERIAN, P.A., HALEY, N.J., SHIO, H. Lysosomes, vascular intracellular lipid accumulation, and atherosclerosis. In: Carlson, L.A., Sirtori, C.R., Paoletti, R., Weber, G. (Editors). *International Conference on Atherosclerosis.* Milan, Italy, November 9–11, 1977, New York, Raven Press, 1978, pp. 19–27.

(50) FRANK, R., BRAUN, H.E., STONFIELD, K.I., ELLIOT, J.M., ZILKEY, B.F. Insecticide residues and metal contents in flue-cured tobacco and tobacco soil of Southern Ontario, 1976–1978. *Tobacco International* 182(23): 59–63, November 1980.

(51) GARDNER, R.S., TOPPING, D.L., MAYES, P.A. Immediate effects of carbon monoxide on the metabolism of chylomicron remnants by perfused rat liver. *Biochemical and Biophysical Research Communications* 82(2): 526–531, May 30, 1978.

(52) GARRETT, R.J.B., JACKSON, M.A. Effect of acute smoke exposure on hepatic protein synthesis. *Journal of Pharmacology and Experimental Therapeutics* 209(2): 215–218, May 1978.

(53) GORDON, T., KANNEL, W.B. Multiple risk functions for predicting coronary heart disease: The concept, accuracy, and application. *American Heart Journal* 103(6): 1031–1039, June 1982.

(54) GORROD, J.W., JENNER, P. The metabolism of tobacco alkaloids. In: Hayes, W.J., Jr. (Editor). *Essays in Toxicology,* Volume 6. Academic Press, New York, pp. 35–78, 1975.

(55) GORROD, J.W., JENNER, P., KEYSELL, G.R., MIKHAEL, B.R. Oxidative metabolism of nicotine by cigarette smokers with cancer of the urinary bladder. *Journal of the National Cancer Institute* 52(5): 1421–1424, May 1974.

(56) GREENHALGH, R.M., LAING, S.P., COLE, P.V., TAYLOR, G.W. Smoking and arterial reconstruction. *British Journal of Surgery* 68(9): 605–607, September 1981.

(57) HALEY, N.J., AXELRAD, C.M., HOFFMANN, D. Experimental atherosclerosis in Syrian golden hamsters. *Cigarette Smoking as a Risk for Cardiovascular Disease.* IV. Manuscript in preparation.

(58) HALEY, N.J., AXELRAD, C.M., TILTON, K.A. Validation of self-reported smoking behavior: Biochemical analyses of cotinine and the thiocyanate. *American Journal of Public Health,* in press.

(59) HALEY, N.J., HILL, P., WYNDER, E.L. Circulating catecholamine levels with patterns of nicotine absorption. *Cigarette smoking as a risk for cardiovascular disease,* IV., in press.

(60) HALEY, N.J., SHIO, H., FOWLER, S. Characterization of lipid-laden aortic cells from cholesterol-fed rabbits. I. Resolution of aortic cell populations by metrizamide density gradient centrifugation. *Laboratory Investigation* 37(3): 287–296, September 1977.

(61) HARDY, D.R., HOBBS, M.E. The use of ^{15}N and of ^{15}N and ^{16}O in added nitrates for the study of some generated constituents of normal cigarette smoke. In: *Recent Advances in the Chemical Composition of Tobacco and Tobacco Smoke.* Proceedings of the American Chemical Society Symposium, the 173d American Chemical Society meeting, Agricultural and Food Chemistry Division, New Orleans, Louisiana, March 20–25, 1977, pp. 489–510.

(62) HEGARTY, K.M., TURGISS, L.E., MULLIGAN, J.J., CLUETTE, J.E., KEW, R.R., STACK, D.J., HOJNACKI, J.L. Effect of cigarette smoking on high density lipoprotein phospholipids. *Biochemical and Biophysical Research Communications* 104(1): 212–219, January 15, 1982.

(63) HENGEN, N., HENGEN, M. Gas-liquid chromatographic determination of nicotine and cotinine in plasma. *Clinical Chemistry* 24(1): 50–53, 1978.

(64) HERNING, R.I., JONES, R.T., BACHMAN, J., MINES, A.H. Puff volume increases when low-nicotine cigarettes are smoked. *British Medical Journal* 283(6285): 187–189, July 18, 1981.

(65) HILL, P., MARQUARDT, H. Plasma and urine changes after smoking different brands of cigarettes. *Clinical Pharmacology and Therapeutics* 27(5): 652–658, May 1980.

(66) HILL, P., WYNDER, E.L. Smoking and cardiovascular disease. Effect of nicotine on the serum epinephrine and corticoids. *American Heart Journal* 87(4): 491–496, April 1974.

(67) HIRSH, P.D., CAMPBELL, W.B., WILLERSON, J.T., HILLIS, L.D. Prostaglandins and ischemic heart disease. *American Journal of Medicine* 71: 1009–1026, December 1981.

(68) HOFFMANN, D., ADAMS, J.D., HALEY, N.J. Reported cigarette smoke values. A closer look. *American Journal of Public Health.* In press.

(69) HOFFMANN, D., ADAMS, J.D., WYNDER, E.L. Formation and analysis of carbon monoxide in cigarette mainstream and sidestream smoke. *Preventive Medicine* 8(3): 344–350, May 1979.

(70) HOFFMANN, D., HALEY, N.J., BRUNNEMANN, K.D., ADAMS, J.D., WYNDER, E.L. *Cigarette Sidestream Smoke: Formation, Analysis, and Model Studies on the Uptake by Nonsmokers.* Paper presented at the U.S.-Japan meeting on "New Etiology of Lung Cancer," Hawaii, March 21–23, 1983, p. 13.

(71) HOJNACKI, J.L., MULLIGAN, J.J., CLUETTE, J.E., KEW, R.R., STACK, D.J., HUBER, G.L. Effect of cigarette smoke and dietary cholesterol on plasma lipoprotein composition. *Artery* 9(4): 285–304, 1981.

(72) HORTON, A.D., GUERIN, M.R. Quantitative determination of sulfur compounds in the gas phase of cigarette smoke. *Journal of Chromatography* 90(1): 63–70, March 13, 1974.

(73) HOUSEMAN, T.H. Studies of cigarette smoke transfer using radioisotopically labelled tobacco constituents. Part II. The transference of radioisotopically labelled nicotine to cigarette smoke. *Beiträge zur Tabakforschung* 7(3): 142–147, November 1973.

(74) HUBERT, H.B., HOLFORD, T.R., KANNEL, W.B. Clinical characteristics and cigarette smoking in relation to prognosis of angina pectoris in Framingham. *American Journal of Epidemiology* 115(2): 231–242, February 1982.

(75) HUGOD, C., ASTRUP, P. Exposure of rabbits to carbon monoxide and other gas phase constituents of tobacco smoke. Influence on coronary and aortic intimal morphology. *Münchener Medizinische Wochenschrift* 122(Supplement 1): S18–S24, February 20, 1980.

(76) HUGOD, C., ASTRUP, P. Studies of coronary and aortic intimal morphology in rabbits exposed to gas phase constituents of tobacco smoke (hydrogen cyanide, nitric oxide and carbonyl sulphide). In: Greenhalgh, R.M. (Editor). *Smoking and Arterial Disease.* London, Pitman Medical, 1981, pp. 89–94.

(77) JARVIK, M.E. Biological factors underlying the smoking habit. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). *Research on Smoking Behavior.* NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM)78–581, December 1977, pp. 122–148.

(78) JENNER, P., GORROD, J.W., BECKETT, A.H. The absorption of nicotine-1-N-oxide and its reduction in the gastro-intestinal tract in man. *Xenobiotica* 3(6): 341–349, June 1973.

(79) JOHNSON, W.R., HALE, R.W., CLOUGH, S.C., CHEN, P.H. Chemistry of the conversion of nitrate nitrogen to smoke products. *Nature* 243(5404): 223–225, May 25, 1973.

(80) JOHNSON, W.R., KANG, J.C. Mechanisms of hydrogen cyanide formation from the pyrolysis of amino acids and related compounds. *Journal of Organic Chemistry* 36(1): 189-192, January 15, 1971.

(81) KAMERLING, S.G., WETTSTEIN, J.G., SLOAN, J.W. SU, T.-P., MARTIN, W.R. Interaction between nicotine and endogenous opioid mechanisms in the unanesthetized dog. *Pharmacology, Biochemistry and Behavior* 17(4): 733-740, October 1982.

(82) KANNEL, W.B. Update on the role of cigarette smoking in coronary artery disease. *American Heart Journal* 101(3): 319-328, March 1981.

(83) KAUFMAN, D.W., HELMRICH, S.P., ROSENBERG, L., MIETTINEN, O.S., SHAPIRO, S. Nicotine and carbon monoxide content of cigarette smoke and the risk of myocardial infarction in young men. *New England Journal of Medicine* 308(8): 409-413, February 24, 1983.

(84) KERSHBAUM, A., BELLET, S., DICKSTEIN, E.R., FINEBERG, L.J. Effect of cigarette smoking and nicotine on serum free fatty acids: Based on a study in the human subject and the experimental animal. *Circulation Research* 9(3): 631-638, May 1961.

(85) KEVANY, J., JESSOP, W., GOLDSMITH, A. The effect of smoking on ascorbic acid and serum cholesterol in adult males. *Irish Journal of Medical Science* 144(12): 474-477, December 1975.

(86) KIEFER, J.E. Ventilated filters and their effect on smoke composition. In: *Recent Advances in Tobacco Science.* Series 4, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York, 1978, pp. 69–83.

(87) KNIKER, W.T., COCHRANE, C.G. The localization of circulating immune complexes in experimental serum sickness. *Journal of Experimental Medicine* 127(1): 119–135, January 1, 1968.

(88) KOCH, A., HOFFMANN, K., STECK, W., HORSCH, A., HENGEN, N., MORL, H., HARENBERG, J., SPOHR, U., WEBER, E. Acute cardiovascular reactions after cigarette smoking. *Atherosclerosis* 35(1): 67–75, January 1980.

(89) KOZLOWSKI, L.T., FRECKER, R.C., KHOUW, V., POPE, M.A. The misuse of "less-hazardous" cigarettes and its detection: Hole-blocking of ventilated filters. *American Journal of Public Health* 70(11): 1202–1203, November 1980.

(90) KRASNEGOR, N.A. (Editor). *Cigarette Smoking as a Dependence Process.* NIDA Research Monograph 23. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, Division of Research, DHEW Publication No. (ADM)79-800, January 1979, 200 pp.

(91) KUHN, H., KLUS, H. Possibilities for the reduction of nicotine in cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker.* Volume I. Proceedings of the Third World Conference on Smoking and Health, New York City, June 2–5, 1975. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76–1221, 1976, pp. 463-494.

(92) LANGONE, J.J., GJIKA, H.B., VAN VUNAKIS, H. Nicotine and its metabolites. Radioimmunoassays for nicotine and cotinine. *Biochemistry* 12(24): 5025-5030, November 20, 1973.

(93) LARSON, P.S., SILVETTE, H. (Editors). *Tobacco, Experimental and Clinical Studies. A Comprehensive Account of the World Literature.* Supplement III. Baltimore, Williams and Wilkins Co., 1975, 798 pp.

(94) LEKAKIS, J., KALOFOUTIS, A. Zinc concentrations in serum as related to myocardial infarction. *Clinical Chemistry* 26(12): 1660–1661, 1980.

(95) LEVINE, P.H. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. *Circulation* 48(3): 619–623, September 1973.

(96) LEVY, R.I., MOSKOWITZ, J. Cardiovascular research: Decades of progress, a decade of promise. *Science* 217(4555): 121–129, July 9, 1982.

(97) LEWIS, G.P., JUSKO, W.J., COUGHLIN, L.L. Cadmium accumulation in man: Influence of smoking, occupation, alcoholic habit and disease. *Journal of Chronic Diseases* 25(12): 717–726, December 1972.

(98) LOW, W.I., IKRAM, H. Plasma zinc in acute myocardial infarction. Diagnostic and prognostic implications. *British Heart Journal* 38(12): 1339–1342, December 1976.

(99) MANTHEY, J., STOEPPLER, M., MORGENSTERN, W., NÜSSEL, E., OPHERK, D., WEINTRAUT, A., WESCH, H., KÜBLER, W. Magnesium and trace metals: Risk factors for coronary heart disease? Associations between blood levels and angiographic findings. *Circulation* 64(4): 722–729, October 1981.

(100) McGILL, H.C., Jr. Potential mechanisms for the augmentation of atherosclerosis and atherosclerotic disease by cigarette smoking. *Preventive Medicine* 8(3): 390–403, May 1979.

(101) MELLION, B.T., IGNARRO, L.J., OHLSTEIN, E.H., PONTECORVO, E.G., HYMAN, A.L., KADOWITZ, P.J. Evidence for the inhibitory role of guanosine 3',5'-monophosphate in ADP-induced human platelet aggregation in the presence of nitric oxide and related vasodilators. *Blood* 57(5): 946–955, May 1981.

(102) MORIE, G.P., MORRISETT, P.E. Determination of transition metals in cigarette smoke condensate by solvent extraction and atomic absorption spectroscopy. *Beiträge zur Tabakforschung* 7(5): 302–303, September 1974.

(103) MUSTARD, J.F. Cigarette smoking, atherosclerosis and its clinical complications. *Canadian Journal of Public Health* 72(6): 385–388, November-December 1981.

(104) NATIONAL CENTER FOR HEALTH STATISTICS. Blood carbon monoxide levels in persons 3–74 years of age: United States 1976–80. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, No. 76, DHHS Publication No. (PHS)82–1250, March 17, 1982, 24 pp.

(105) NORMAN, V. The effect of perforated tipping paper on the yield of various smoke components. *Beiträge zur Tabakforschung* 7(5): 282–287, September 1974.

(106) NORMAN, V. An overview of the vapor phase, semivolatile and nonvolatile components of cigarette smoke. *Recent Advances in Tobacco Science.* Series 3. Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York, 1977, pp. 28–58.

(107) NORMAN, V. Changes in smoke chemistry of modern day cigarettes. *Recent Advances in Tobacco Science* 8: 141–177, 1982.

(108) OESTERGAARD, K. Renal cadmium concentration in relation to smoking habits and blood pressure. *Acta Medica Scandinavica* 203(5): 379–383, 1978.

(109) OHANIAN, E.V., IWAI, J. Etiological role of cadmium in hypertension in an animal model. *Journal of Environmental Pathology and Toxicology* 4(2–3): 229–241, September 1980.

(110) OHANIAN, E.V., IWAI, J., LEITL, G., TUTHILL, R. Genetic influence on cadmium-induced hypertension. *American Journal of Physiology* 235(4): H385–H391, October 1978.

(*111*) OWENS, W.F., Jr. Effect of cigarette paper on smoke yield and composition. *Recent Advances in Tobacco Science.* Series 4. Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York, 1978, pp. 3–24.

(*112*) PACHINGER, O., HELLBERG, K.D., BING, R.J. The effect of nicotine, propranolol, phentolamine and hexamethonium on the coronary microcirculation of the cat. *Journal of Clinical Pharmacology* 12(11–12): 432–439, November-December 1972.

(*113*) PERRY, H.M., Jr., ERLANGER, M., PERRY, E.F. Elevated systolic pressure following chronic low-level cadmium feeding. *American Journal of Physiology* 232(2): H114–H121, February 1977.

(*114*) PHILIPPE, R.J., MOORE, H. The semi-quantitative determination of methyl thionitrite and carbon disulfide in cigarette smoke. *Tobacco Science* 5: 121–124, 1961.

(*115*) PLEBAN, P.A., KERKAY, J., PEARSON, K.H. Cadmium, copper, lead, manganese, and selenium levels, and glutathione peroxidase activity in human kidney cortex. *Analytical Letters* 14(B13): 1089–1109, 1981.

(*116*) PRYOR, W.A., CHURCH, D.F., GOVINDAN, C.K., CRANK, G. Oxidation of thiols by nitric oxide and nitrogen dioxide: Synthetic utility and toxicological implications. *Journal of Organic Chemistry* 47(1): 156–159, January 1, 1982.

(*117*) RABKIN, S.W., BOYKO, E., STREJA, D.A. Relationship of weight loss and cigarette smoking to changes in high-density lipoprotein cholesterol. *American Journal of Clinical Nutrition* 34(9): 1764–1768, September 1981.

(*118*) RAYMOND, T.L., DELUCIA, A.J., BRYANT, L.R. Failure of chronic cigarette smoke exposure to alter plasma lipoproteins of stumptailed macaques (*Macaca arctoides*). *Atherosclerosis* 41(1): 27–33, January 1982.

(*119*) REVIS, N.W., MAJOR, T.C., HORTON, C.Y. The effects of calcium, magnesium, lead, or cadmium on lipoprotein metabolism and atherosclerosis in the pigeon. *Journal of Environmental Pathology and Toxicology* 4(2–3): 293–303, September 1980.

(*120*) RICKERT, W.S., ROBINSON, J.C. Yields of selected toxic agents in the smoke of Canadian cigarettes, 1969 and 1978. A decade of change? *Preventive Medicine* 10(3): 353–363, May 1981.

(*121*) ROHRER, S.R., SHAW, S.M., LAMAR, C.H. Cadmium induced endothelial cell alterations in the fetal brain from prenatal exposure. *Acta Neuropathologica* 44(2): 147–149, 1978.

(*122*) ROSS, R. Platelets, smooth muscle proliferation, and atherosclerosis. *Acta Medica Scandinavica* (Supplementum 642): 49–54, 1980.

(*123*) ROSS, R., GLOMSET, J.A. The pathogenesis of atherosclerosis. First of two parts. *New England Journal of Medicine* 295(7): 369–376, August 12, 1976.

(*124*) ROSS, R., GLOMSET, J.A., HARKER, L. Response to injury and atherogenesis. *American Journal of Pathology* 86(3): 675–684, March 1977.

(*125*) ROSS, R., HARKER, L. Hyperlipidemia and atherosclerosis. Chronic hyperlipidemia initiates and maintains lesions by endothelial cell desquamation and lipid accumulation. *Science* 193(4258): 1094–1100, September 17, 1976.

(*126*) ROTH, R.A., Jr., RUBIN, R.J. Comparison of the effect of carbon monoxide and of hypoxic hypoxia. I. *In vivo* metabolism, distribution and action of hexobarbital. *Journal of Pharmacology and Experimental Therapeutics* 199(1): 53–60, October 1976.

(*127*) RUSSELL, M.A.H. The case for medium-nicotine, low-tar, low-carbon monoxide cigarettes. In: Gori, G.B., Bock, F.G. (Editors), *Banbury Report 3—A Safe Cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 297–310.

(*128*) RYLANDER, R. Free lung cell studies in cigarette smoke inhalation experiments. *Scandinavian Journal of Respiratory Diseases* 52(2): 121–128, 1971.

(*129*) SCHIEVELBEIN, H., EBERHARDT, R. Cardiovascular actions of nicotine and smoking. *Journal of the National Cancer Institute* 48(6): 1785–1794, June 1972.

(*130*) SCHMELTZ, I., WENGER, A., HOFFMANN, D., TSO, T.C. Chemical studies on tobacco smoke. 63. On the fate of nicotine during pyrolysis and in a burning cigarette. *Journal of Agricultural and Food Chemistry* 27(3): 602–608, May-June 1979.

(*131*) SCHROEDER, H.A. Cadmium as a factor in hypertension. *Journal of Chronic Diseases* 18: 647–656, July 1965.

(*132*) SEPKOVIC, D.W., HALEY, N.J., AXELRAD, C.M., WYNDER, E.L. Cigarette smoking as a risk for cardiovascular disease III. Biomedical effects with higher nicotine yield cigarettes. *Addictive Behaviors* 8(1): 59–66, 1983.

(*133*) SILVETTE, H., HOFF, E.C., LARSON, P.S., HAAG, H.B. The actions of nicotine on central nervous system functions. *Pharmacological Reviews* 14(1): 137–173, March 1962.

(*134*) SLOAN, C.H., KIEFER, J.E. Determination of NO and NO_2 in cigarette smoke from kinetic data. *Tobacco Science* 13: 180–182, December 26, 1969.

(*135*) SPOHR, U., HARENBERG, J., WALTER, E., AUGUSTIN, J., MÖRL, H., KOCH, A., WEBER, E. Smoking-induced effects on circulatory and metabolic variables with respect to plasma nicotine and COHb levels. In: Greenhalgh, R.M. (Editor). *Smoking and Arterial Disease.* London, Pitman Medical, 1981, pp. 98–106.

(*136*) STIMMEL, B. *Cardiovascular Effects of Mood-Altering Drugs.* New York, Raven Press, 1979, 290 pp.

(*137*) STRONG, J.P., SOLBERG, L.A., RESTREPO, C. Atherosclerosis in persons with coronary heart disease. *Laboratory Investigation* 18(5): 527–537, May 1968.

(*138*) THOMAS, M. Smoking and vascular surgery. *British Journal of Surgery* 68(9): 601–604, September 1981.

(*139*) TIGGELBECK, D. Improved cigarettes—Comments on the state-of-the-art, 1971. *Journal of the National Cancer Institute* 48(6): 1825–1832, June 1972.

(*140*) TSO, T.C. *Physiology and Biochemistry of Tobacco Plants.* Stroudsburg, Pa., Dowden, Hutchinson and Ross, Inc., 1972, 393 pp.

(*141*) TSO, T.C. Tobacco as a potential food source and smoke material. *Beiträge zur Tabakforschung* 9(2): 63–66, June 1977.

(*142*) TURINO, G.M. Effect of carbon monoxide on the cardiorespiratory system. Carbon monoxide toxicity: Physiology and biochemistry. *Circulation* 63(1): 253A–259A, January 1981.

(*143*) TURNER, D.M., ARMITAGE, A.K., BRIANT, R.H., DOLLERY, C.T. Metabolism of nicotine by the isolated perfused dog lung. *Xenobiotica* 5(9): 539–551, September 1975.

(*144*) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79–50066, 1979, 1136 pp.

(*145*) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking. Cancer: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health. DHHS Publication No. (PHS)82–50179, 1982, 322 pp.

(146) U.S. FEDERAL TRADE COMMISSION. *"Tar," Nicotine and Carbon Monoxide of the Smoke of 208 Varieties of Domestic Cigarettes.* Washington, D.C., U.S. Federal Trade Commission, March 1983, 19 pp.

(147) VAN HOUTE, O., KESTELOOT, H. An epidemiological survey of risk factors for ischemic heart disease in 42,804 men. I.—Serum cholesterol value. *Acta Cardiologica* 27(5): 527–564, 1972.

(148) VESTAL, R.E., NORRIS, A.H., TOBIN, J.D., COHEN, B.H., SHOCK, N.W., ANDRES, R. Antipyrine metabolism in man: Influence of age, alcohol, caffeine, and smoking. *Clinical Pharmacology and Therapeutics* 18(4): 425–432, October 1975.

(149) VILCINS, G., LEPHARDT, J.O. Aging processes of cigarette smoke: Formation of methyl nitrite. *Chemistry and Industry* 22: 974–975, November 15, 1978.

(150) VON AHN, B. Tobacco smoking, the electrocardiogram, and angina pectoris. *Annals of the New York Academy of Sciences* 90(1): 190–198, 1960.

(151) WAGNER, J.R., THAGGARD, N.A. Gas-liquid chromatographic determination of nicotine contained on Cambridge filter pads: A collaborative study. *Journal of the Association of Official Analytical Chemists* 62(2): 229–236, March 1979.

(152) WALD, N., HOWARD, S., SMITH, P.G., KJELDSEN, K. Association between atherosclerotic diseases and carboxyhaemoglobin levels in tobacco smokers. *British Medical Journal* 1(5856): 761–765, March 31, 1973.

(153) WALD, N., IDLE, M., SMITH, P.G., BAILEY, A. Carboxyhaemoglobin levels in smokers of filter and plain cigarettes. *Lancet* 2(8003): 110–112, January 15, 1977.

(154) WARTMAN, W.B. Jr., COGBILL, E.C., HARLOW, E.S. Determination of particulate matter in concentrated aerosols. Application to analysis of cigarette smoke. *Analytical Chemistry* 31(10): 1705–1709, 1959.

(155) WENNMALM, A. Nicotine stimulates prostaglandin formation in the rabbit heart. *British Journal of Pharmacology* 59(1): 95–100, January 1977.

(156) WENNMALM, A. Nicotine inhibits hypoxia- and arachidonate-induced release of prostacyclin-like activity in rabbit hearts. *British Journal of Pharmacology* 69(4): 545–549, August 1980.

(157) WENNMALM, A. Interaction of nicotine and prostaglandins in the cardiovascular system. *Prostaglandins* 23(1): 139–144, January 1982.

(158) WENZEL, D.G., REED, B.L. Measurement of lysosomal fragility produced by hypoxia, nicotine, carbon monoxide, and hyperoxia in cultured endothelioid cells. *Research Communications in Chemical Pathology and Pharmacology* 7(4): 745–754, April 1974.

(159) WESTFALL, T.C., BRASTED, M. The mechanism of action of nicotine on adrenergic neurons in the perfused guinea-pig heart. *Journal of Pharmacology and Experimental Therapeutics* 182(3): 409–418, September 1972.

(160) WOLINSKY, H. A proposal linking clearance of circulating lipoproteins to tissue metabolic activity as a basis for understanding atherogenesis. *Circulation Research* 47(3): 301–311, September 1980.

(161) WOOLF, M., WILSON-HOLT, N.J. Cigarette smoking and atherosclerosis. In: Greenhalgh, R.M. (Editor). *Smoking and Arterial Disease.* London, Pitman Medical, 1981, pp. 46–59.

(162) WYNDER, E.L., HOFFMANN, D. *Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis.* New York, Academic Press, 1967, 730 pp.

(163) ZENZ, C. The epidemiology of carbon monoxide in cardivoascular disease in industrial environments: A review. *Preventive Medicine* 8(3): 279–288, May 1979.

SECTION 7. CHANGES IN CIGARETTE SMOKING BEHAVIOR IN CLINICAL AND COMMUNITY TRIALS

Introduction

This section examines the changes in cigarette smoking behavior resulting from intervention strategies. The next section presents detailed data on CHD outcome resulting from these trials compared with those prospective epidemiologic studies for which cessation outcome information is available.

Large-scale primary preventive trials have used both single and multifactorial intervention in high risk populations in an attempt to test the effect of the modification of major risk factors, either alone or in combination, on coronary heart disease (CHD) or respiratory disease. Several of these trials have been developed and implemented since the early 1970s, and provide a valuable opportunity for assessing the efficacy and outcomes of smoking intervention techniques in particular high risk populations and the impact of smoking behavior change on disease. The objective of this section is to present and critically appraise the smoking intervention programs and the smoking cessation outcomes in the large-scale controlled preventive trials.

At present there are two types of preventive trials in cardiovascular or respiratory disease that either have been completed or are currently in progress. One type includes *clinical investigations* in which *individuals* are randomized either to an intervention group for a risk factor reduction program or to their usual source of medical care. These randomized trials are either single factor trials that intervene on one variable such as cigarette smoking, as in the London Civil Servants smoking trial (*55, 60, 61*), or multifactorial trials that generally attempt to change the alterable risk factors of cigarette smoking, hypercholesterolemia, and hypertension, or some combination of these risk factors. In this group are the Göteborg (Sweden) trial (*78, 79, 80*), the Oslo (Norway) study (*16, 17*), and the Multiple Risk Factor Intervention Trial (MRFIT) (*19, 43*).

The randomization of *entire populations* to an intervention or a no-intervention group comprises the second type of trial. In this group of *community investigations* are trials based on random allocation of factories to intervention or regular care, as in the WHO study (*62*), which involves four centers—London, Brussels/Ghent, Rome, and Warsaw—using a common protocol, and trials in which entire geographic areas are randomized, as in the North Karelia project (*52, 53, 54, 63, 64, 65*). Although the Stanford study has been described by its investigators as a community-based investigation (*13, 14, 36, 41*), it did not involve random allocation of communities and thus does not belong in this group as defined here. Although the Stanford group studied three different communities, individuals within one community were randomized to intensive or to community intervention only. Therefore, for the purposes of this review, the

Stanford study will be included with the first group of trials, although it somewhat overlaps both groups.

Smoking intervention methods and smoking behavior change outcomes for each of these trials will be presented and critically evaluated. These prospective studies use experimental design methodology that maximizes comparability of treated and untreated groups by maintaining a high degree of quality control on all aspects of randomization, data collection, and evaluation; by utilizing unbiased statistical treatment of the data; and by detailing a priori specification of the intervention (*38*).

A major problem in assessing outcomes of smoking intervention studies has been research that has often been poor in methodology, quality control, and design. Although preventive trials have generally conformed to the desired methodology as noted above, they too, as with other smoking intervention studies, have been deficient in some of the methods used or in the reporting of the data. The deficiencies of smoking intervention studies have been well reviewed in past investigations (*5, 34, 45, 67*) and will be only briefly summarized here to provide a basis on which to critically review the research and smoking intervention designs in preventive trials.

Problems in Smoking Intervention Studies

Lack of Objective Data to Verify Self-Reported Outcomes

A major deficiency in smoking cessation evaluation research has been the use of self-reported smoking data that have not been validated with objective measures. These data depend on the subjects' honest and accurate reporting and often lead to an overestimation of success, especially among participants who feel the pressure to stop smoking, as in an intervention program. Neaton et al. (*46*) found that when the reported quit-rate of the intervention group in MRFIT was adjusted using serum thiocyanate (SCN) levels, the overreporting ranged from 5 to 9 percent, while a much smaller overreporting rate was found in the usual care group not treated in the program. The demand characteristics of the intervention program may prompt some individuals to falsely comply with the expectations of the interventionist (*2*).

One approach to validation of self-reported data involves the use of serum thiocyanate (SCN) determinations as objective measures of smoking status, with a critical cutoff point used to differentiate smokers from nonsmokers (*3*). SCN is the metabolite of hydrogen cyanide, a pyrrolic product in tobacco smoke. In addition to cigarette smoking, SCN may be elevated by the use of pipes, cigars, or cigarillos. However, the interpretation of SCN concentration is potentially confounded by at least two factors. Certain foods, particularly those of the Brassica genus (cabbage, cauliflower, kale,

kohlrabi, broccoli, brussels sprouts, turnips, and rutabagas), as well as fruit pits and almonds, may elevate levels. Also, diuretics tend to raise SCN levels by an average of 8 μmol/liter (*51*). With such limitations in mind, the biologic half-life of SCN, approximately 14 days (*51*), still makes it a measure well suited for corroboration of self-reports. Determinations of SCN in saliva and urine have also been used and are more adaptable to some settings (*11, 42*). Measurement of carbon monoxide (CO) concentrations in serum or expired air also can be used as a validation tool (*29, 57, 76*). The major drawback of this measure is CO's short half-life of several hours (*56, 72*); it may also be affected by various environmental factors (*72, 77*).

The most specific objective indicator of tobacco use is nicotine itself or its major metabolite cotinine, both of which can be measured in blood, saliva, or urine (*21, 31*). The extremely short half-life of nicotine, on the order of 30 minutes, makes it unsuitable for verification of cessation or for quantifying estimates of tobacco intake, but the 20- to 30-hour half-life of cotinine is much more useful for these purposes (*4, 82*). Unfortunately, cotinine analyses are rarely used in clinical trials because of the expense and the relative unavailability of the complex analytic technique compared with SCN determination.

Lack of Comparison Groups

Only recently have clinical assessments of smoking in intervention programs been more consistent in their use of an experimental design that includes random allocation to the experimental smoking cessation condition or to an appropriate comparison group. Investigators using a minimal treatment or attention–placebo comparison group have demonstrated that these groups produce smoking cessation results beyond those that no intervention would be expected to produce (*28, 32, 37*). These outcomes have been partially accounted for by certain "nonspecific factors" common to all treatment settings and cannot be attributed to a specific intervention technique. These nonspecific factors include the use of self-monitoring, a structured program that promotes the expectation of success, and a therapist's attention (*1, 5, 40*). Determination of the effect of a proposed treatment on outcome results is not possible without rigorous designs that include appropriate experimental controls, preferably a minimal-treatment control group (*37*).

Classification Differences

Smoking control studies use variable criteria for grouping individuals; this makes it difficult to compare outcomes. For example, Straits' (*73*) successes achieved at least an 85 percent reduction in smoking, whereas Keutzer's (*25*) successes achieved at least a 50

percent reduction. Kanzler et al.'s (*23*) "continuing successes" (3 1/2 to 4 years after treatment) were subjects who had not recidivated at any time for "longer than a week," while Ockene et al.'s (*50*) "continuing successes" were at zero cigarettes for at least 2 years, and self-reports were validated with SCN measurements.

Similarly, in some studies a smoker is someone who smokes pipes, cigars, or cigarettes (e.g., Oslo study), while in other studies a subject is classified as a smoker on the basis of whether or not he or she smokes cigarettes only (e.g., MRFIT). Because of the lack of consistency in groups compared and criteria used, outcomes of studies are difficult to evaluate, and cross-validation can provide onflicting outcomes. In order to avoid these problems, standard classification categories have been suggested (*69*).

Followup Differences and Deficiencies

Experimental studies of smoking have used different followup points to assess outcomes and to determine predictor variables. These followup points have included immediately post-treatment (*25*), 2 weeks' post-treatment (*1*), 3-month followup (*22*), 6-month followup (*6*), 1-year followup (*70*), and 3- to 4-year followup (*23, 30, 50*). In most studies, cessation rates at followup points refer to "nonsmoking prevalence" at that point in time, rather than to continued abstinence from immediately post-treatment onward. Such studies give no indication of the dynamics of cessation and relapse that determine the nonsmoking prevalence rate, nor do they indicate what is happening long term with a cohort of smokers. Ockene et al. (*48, 49*), in their analyses of the smoking data from the Multiple Risk Factor Intervention Trial (MRFIT), demonstrate the importance of following cohorts of smokers from baseline to followup points in addition to determining cessation rates at a single point in time. Careful definition of cessation rates should be given in all research reports so that the reader can distinguish whether a given rate refers to a single probe measure or to a quit status of some known duration. Shipley et al. (*71*) have discussed this problem in depth and offered potential standards for reporting in the smoking cessation literature.

Because of the high recidivism rate in the first year of abstinence (*20*), the comparison of a study that measures cessation at immediate post-treatment to one that assesses cessation at 1-year post-treatment will demonstrate very different outcomes. As explained above, the smoker reporting cessation at immediate post-treatment could become either a continuing success or a recidivist at 1-year post-treatment. In effect, comparing stoppers at different points is similar to comparing different groups (*47*). The smoker's continuing susceptibility to relapse, even after being cigarette free for more than 2 years, needs to be reflected in smoking research and intervention by

the inclusion of followup and maintenance programs beyond the usual 6 to 12 months (*49*).

Most studies also fail to note whether a followup point (e.g., 1 year) indicates a period of time since the entire study began or since the smoker entered the program. If it indicates the former, it is possible that there is a different length of followup for participants in the same study, depending on when they entered the program. Outcomes for these participants should not be compared unless appropriate analytic techniques such as life tables (*7*) or person-years (*7*) are used to adjust for the differing lengths of followup.

Methods of Data Reporting

The continuing susceptibility of the smoker to relapse, as well as the fact that it is long-term rather than short-term cessation that has an impact on disease outcomes (*48, 49*), needs to be reflected in the way data are reported in smoking cessation research, although this rarely occurs. Cross-sectional cessation data are generally measured and reported giving little indication of the dynamics of cessation and relapse that determine the cessation rate at any one point in time (*49*). Thus, a cessation rate of 30 percent at 2-year followup does not mean that 30 percent of the smokers in a study remained cigarette free for 2 years. Perhaps only 10 percent were nonsmokers for the entire 2-year period. Studies of smokers quitting both with and without formalized aid show that people often pass through several cycles of cessation and relapse before permanent cessation is achieved (*10, 56*). Analysis of data from cohorts of baseline smokers followed longitudinally provides a more complete understanding of smoking behavior change and "true" long-term cessation. It also provides relevant data for evaluating the effect of cessation on disease outcome. Cohort analyses are missing in all but a very few studies.

The primary evaluation of treatment results should be based on abstinence data for several reasons, as summarized by Pechacek (*75*), including the following: abstinence is the primary goal of most smokers enrolled in programs; smoking behavior change followup data have indicated that most smokers who reduce their smoking without totally stopping return to baseline smoking levels; a clinically insignificant proportion of smokers at followup can be abstinent and yet analyses of rate data can show statistically significant treatment effects; and reports of abstinence rather than reduction are less susceptible to exaggeration and the demands of the program placed on the smoker. In spite of the importance of cessation data and of true long-term data, these are often missing in outcome reports.

The Use of Various Methods for the Determination of Treatment Outcomes

Methods for determining treatment outcomes include telephone calls (*23*), in-person interviews (*19, 70*), and mailed questionnaires (*12*). The variability of the groups of smokers reached by these different methods and their effects changes the criterion groups and can be responsible for an extraneous source of variance leading to distortion of the comparisons. Those subjects who respond immediately to smoking behavior assessment or followup are more often ex-smokers, but those reached only after repeated tries are often smokers (*68*). Therefore, the success and failure groups in a study in which there is a high followup response (*19, 47, 70*) may be quite different from these same groups in a study with a followup response of less than 50 percent (*23*). It would be valuable to pursue a random sample of nonresponders in order to be able to study and compare responders with nonresponders in terms of generalizability of outcomes.

Lack of Information and Precautions Needed to Adequately Interpret Outcomes

A smoking cessation program or trial cannot be adequately evaluated or interpreted without sufficient information about the methods used in the design and implementation of the study, the data included for determination of outcomes, and the methods used for the analysis of the outcomes (*9*). DerSimonian et al. (*9*) surveyed 67 clinical trials reported in 4 well-respected medical journals, and found that only 56 percent were clearly reported with respect to 11 important variables. The 11 variables were selected with regard to their importance in determining the confidence that a reader could place in the author's conclusions, their ability to be discerned by the scientifically literate general medical reader, and their applicability across a variety of medical specialties.

A related point specifically aimed at the clinical trials reviewed in this section is the need to specify all treatments other than smoking cessation (e.g., modification of other risk factors) that participants received. What precautions should be taken comparing smoking cessation results from a trial modifying only smoking behavior to a trial simultaneously modifying several risk factors? Specific as well as nonspecific treatment differences are probably operative on outcomes.

In summary, a critical evaluation of any smoking intervention program needs to consider the deficiencies inherent in the study and data analysis design as well as the deficiencies manifested in the study report by the lack of adequate information. Precautions regarding comparison with other studies and generalizations should also be considered. In the following section, the eight major large-

scale preventive trials implemented since 1970 that include a smoking intervention component and have reported smoking cessation outcomes will be reviewed. (Three-year followup data are available for most of the trials; therefore, whenever possible these data will be presented in addition to whatever other data are available and relevant for comparisons.)

Individual Allocation Trials

Single Factor Controlled Clinical Trials

The London Civil Servants Smoking Trial

The participants in the London Civil Servants smoking trial were drawn from the 16,016 men, aged 40 to 59, who had undergone a cardiorespiratory screening examination in the Whitehall study of London Civil Servants carried out between 1968 and 1970 (*55, 60, 61*). The results of the screening were used to select smokers for the trial who had the highest risk of CHD or chronic bronchitis or both, based on a risk score calculated from the multivariate combination of risk factors (*60, 61*). Men were excluded if they had heart disease, severe hypertension (DBP$>$115 mm Hg), diabetes mellitus, or major concomitant disease; were taking psychotropic drugs; or had a history of previous inpatient psychiatric treatment. The selected men were randomly allocated to an intervention group (IG) or to a "normal care" (NC) group. The results were first sent to the participants' general practitioners, who had the opportunity to withdraw their patients from the study. Random allocation resulted in an intervention group of 714 men and a control group of 731 men (Table 1). The two groups were well balanced on all characteristics measured, with a mean age of approximately 53 years and a mean number of cigarettes smoked of 19 in the two comparison groups.

The smokers randomized to the intervention group were sent a letter inviting them to come and discuss "one or two points personally with a physician" (*58*). This session took about 15 minutes, and the smokers were advised of the health gains of cessation rather than the dangers of continuation and then asked to decide if they wanted further help and support (*58, 59, 60*). Booklets prepared for the study were handed out at this visit. Most men indicated that they would like help and were seen on an average of three more visits in the first 10 weeks, and then at 6 months, with each visit taking about 15 minutes. The only other health advice given was on calorie restriction for those who gained weight. Close contact was maintained over several months, and help was available for those smokers who continued to need it. A special substudy was implemented in which a group of intervention participants were randomly allocated either to the usual procedure of further contact

TABLE 1.—Population, randomization, and baseline smoking data for five major controlled clinical trials

Clinical trial (duration)	Population	Randomization methods/ study groups	Baseline age and smoking data
London Civil Servants Smoking Trial (*60, 61*) (10 years)	1,445 healthy males Aged 40–59 High risk for CHD and/or chronic bronchitis based on risk score	Randomized to smoking intervention or normal care Intervention (IG) = 714 males Normal care (NC) = 714 males	$\bar{X}$ age = 53 $\bar{X}$ cigs = 19
Göteborg (Sweden) Study (*78, 79, 80*) (4 years) (Screening 1970–1974) (Reexamination: 1974–1977)	30,000 males Aged 47–54 Living in Göteborg	Randomized to intervention for smoking, hypertension, hypercholesterolemia, and low physical activity; or to control group Intervention group (IG) = 10,000 males Two control groups (CG) = 20,000 males	$\bar{X}$ age = 51 $\bar{X}$ cigs = ? 65% of 7,455 screened in IG were smokers 16% of IG smoked $\geq$15 cigs/day
Oslo (Norway) Study (*16, 17, 18*) (5 years)	1,232 healthy normotensive males Aged 40–59 Upper quartile CHD risk based on risk score	Randomized to intervention for smoking and cholesterol; or to control group Intervention group (I) = 604 males Control group (C) = 628 males	$\bar{X}$ age = 45 $\bar{X}$ cigs (I) = 12.5 $\bar{X}$ cigs (C) = 13.0 80% were smokers

TABLE 1.—Continued.

Clinical trial (duration)	Population	Randomization methods/ study groups	Baseline age and smoking data
Multiple Risk Factor Intervention Trial (MRFIT) *(19, 43)* (1974–1982)	12,866 healthy males Aged 35–37 Top 10–15% risk for CHD based on risk score	Randomized to intervention for smoking, cholesterol, and/or blood pressure; or to control group Special intervention (SI) = 6,428 males Usual care (UC) = 6,428 males	$\bar{X}$ age = 46 $\bar{X}$ cigs = 21 64% were smokers $\bar{X}$ cigs (smokers) = 34
Stanford Three Community Study *(36, 41, 44)* (1972–1975)	Residents of Watsonville, Gilroy, and Tracy, in California Random sample of 500 residents assessed in each community (ages 35–59) Upper quartile of CHD risk selected from random samples	Communities matched, not randomized Watsonville high risk sample randomized: media only (W-RC) = 56 ppts. media and intensive instruction (W-II) = 113 ppts. Gilroy: media only (GMO) = 136 ppts. Tracy: control (C) = 136 ppts.	$\bar{X}$ age (35–59 sample) = approx. 47 $\bar{X}$ cigs (high risk sample) = approx. 14

by personal consultations or to further contact by mailed personal responses from the physician (*58, 59*).

In the initial stage of the trial no contact was made with the control subjects, who were at no time made aware of their high risk status or participation in the trial (*58, 60*). Intervention and control groups were invited in for a physical examination at 1, 3, and 9 years. They were also sent a self-administered questionnaire on current smoking habits, symptoms, and recent illnesses at years 1, 3, and 9. When the control group smokers were invited for the 1-year examinations, they were told that their names were included in a "statistically chosen sample" (*58*). At 1-year followup, 19 percent of the smokers in both groups did not attend, and a similar loss to followup rate was true for the intervention group at 9 years (*59, 61*).

No objective measures were used in this trial to validate self-reported cigarette smoking behavior. On the basis of the self-reports, there was a cigarette smoking cessation rate of 51 percent for intervention group smokers at 1-year followup (nonattendee baseline smokers were included as smokers) (Table 2). Only 31 percent reported cessation of all tobacco, as many had switched to pipes and cigars (*58*). Of all of the men who stopped smoking cigarettes by the end of year 1, 80 percent reported doing so immediately after the first interview (*60*). At 3 years the reported cessation rate went down to 36 percent, perhaps partly owing to the drop in attendance at examinations and in return of questionnaires (i.e., only 64 percent returned for assessment and nonattendees are included at baseline levels).

A comparison of the intervention subgroups who were contacted by mail with those who had a personal consultation indicates that outcome was significantly poorer when the personal contact was omitted, with a 59 percent cessation rate at 10 weeks for the personal contact group and a 46 percent cessation rate for the postal contact group (*62*).

In the normal care group, 10 percent of the total smokers reported cessation at year 1 and 14 percent at year 3. Only 70 percent of the normal care group returned for the third-year examination. At 1 year and 3 years, respectively, there is a 41 and 22 percent net difference in intervention versus control group reported cigarette smoking cessation rates. At 9 years, the return rate for intervention men was 83 percent, with 55 percent reporting cessation, producing a 46 percent reported cessation rate for all baseline smokers (*62*). About one-third of the cigarette abstainers continued to smoke pipes and cigars. The final 9-year smoking cessation rates have not been reported for the normal care group, but cessation rates reported in a postal survey to which 60 percent of the survivors responded indicated that 41 percent of the normal care respondents reported that they were no longer smoking. As these figures have been

TABLE 2.—Intervention, followup, and cessation results for five major controlled clinical trials

Clinical trial	Intervention	Control group contact	Followup	Reported cessation rates/ (objective measures)
London Civil Servants Smoking Trial (*58, 59, 60*)	Letter inviting ppt. to meet with MD Initial 15 min session Three more 15 min visits (with MD) in 10 weeks 6 mo visit Additional help if needed	Not told of high risk status or trial participation	Physical exams & smoking & medical Hx questionnaire at 1, 3, & 9 yrs for both groups Missed visit rates IG NC Year 19% 19% 1 30% 30% 3 17% — 9	Treated Control Time 51%[1] (cigs) 10% (cigs) 1 yr 31% (all smoking) 36% (cigs) 14% (cigs) 3 yrs 46% (cigs) — 9 yrs (no objective measures used)
Göteborg (Sweden) Study (*78*)	Smokers ≥ 15 g tobacco/day invited to antismoking clinic Five biweekly small group sessions 2d session: ppts. given nicotine chewing gum Followup letters at 3, 5, 12 mo	Baseline smoking & medical Hx questionnaire sent to all ppts. in one CG 2% random sample of one CG screened	Physical exams & smoking & medical Hx questionnaire at 4 yrs for all IG males & all males in one CG No missed visit rates noted	31%[1] 26% 4 yrs (no objective measures used)

TABLE 2.—Continued.

Clinical trial	Intervention	Control group contact	Followup	Reported cessation rates/ (objective measures)
Oslo (Norway) Study (*16, 17*)	Initial 15 to 20 min session with MD Group session for men with wives "5-day smoking cessation program" halfway through for those who cont. to smoke 6 mo exam & contact for smoking intervention	Yearly examination	IG: Physical exam & assessment every 6 mos CG: same as above each year Missed visit rate: 1% at 5 yrs for males still living	29% (cigs) 13% (cigs) 3 yrs 31% (cigs) 18% (cigs) 5 yrs 18% (all tobacco) 1% (all tobacco) (measured SCN at end, but rates not reported)
Multiple Risk Factor Intervention Trial (MRFIT) (*48*)	Session with MD at 3d screen Ten group intervention sessions for all risk factors Maintenance protocol if stopped smoking cigs Extended intervention protocol if still smoking Followup at least every 4 mos	Three screening visits Yearly exam & assessments Results sent to MD	SI: every 4 mos for at least 6 yrs UC: yearly exam & assessment for at least 6 yrs Missed visit rates SI UC Year 4.5% 5.2% 1 10% 10% 6	40%[a] 13% 1 yr (29% SCN adjusted) (11% SCN adjusted) 40%[a] 16% 3 yrs (35% SCN adjusted) (15% SCN adjusted) 43%[a] 26% 6 yrs (42% SCN adjusted) (24% SCN adjusted)

TABLE 2.—Continued.

Clinical trial	Intervention	Control group contact	Followup	Reported cessation rates/ (objective measures)
Stanford Three Community Study (*36, 41*)	Media: TV, radio, posters, mail, phone, newspapers Face-to-face intervention: group sessions 10 wks, then biweekly, yr 1 Continued intervention for yrs 2 & 3	Baseline survey (physical + interview) 1st, 2d, & 3d yr surveys repeated: 40 min contact Medical results sent to MD	Surveys (physical + interviews) yrs 1, 2, & 3 High nonattendance rate each yr Highest rate for WII group	Year 3 WII: 32% cessation [3] W-RC: 0% cessation GMO: 11.3% cessation (nonattenders excluded) TC: 14.9% cessation (nonattenders excluded) (SCN measured, but not used to adjust cessation rates)

[1] $P \leq 0.05$.

[2] Not significant.

[3] $P \leq 0.01$.

IG: Intervention Group; CG: Control Group; SI: Special Intervention group; UC: Usual Care group; WII: Watsonville Intensive Intervention group; W-RC: Watsonville media-only group; GMO: Gilroy media-only group; TC: Tracy Control group.

obtained with different means at 9-year followup, they cannot be compared.

During the first year of the trial, the reported number of cigarettes smoked fell dramatically for the intervention group from 19 cigarettes per day to about 4 cigarettes per day, which was about one-quarter of the consumption of the control group. There was a steady decrease over the next 9 years in the number of cigarettes smoked by the control group, but there was a steady increase for the intervention group. The net apparent reduction in number of cigarettes smoked at 9 years was 7.6 cigarettes for the intervention group (*62*).

Multifactor Clinical Trials

The Göteborg (Sweden) Primary Prevention Trial

The Göteborg study (*78, 79, 80*), a 4-year multifactor clinical trial, began in 1970 and was designed to determine whether alteration of the risk factors of smoking, hypertension, hypercholesterolemia, and to some degree, low physical activity in men aged 47 to 54 would lower the incidence of CHD and stroke in a random sample (*78, 79, 80*). At the time that the study began, 30,000 men aged 47 to 54 were living in Göteborg. One-third of them, 10,000 men, were randomized into an intervention group, and the other 20,000 were placed into two control groups (Table 1). Screening took place between 1970 and 1973, and reexamination took place between 1974 and 1977. All men in the intervention group and in one control group were sent a questionnaire that included an assessment of smoking and symptoms of CHD and family history. All men in the intervention group were invited to a baseline health checkup; a 2 percent random sample of men in one control group was also screened to assure comparability to the intervention group. At the 4-year followup, all intervention men and men in one control group returned for a physical examination and questionnaire assessment (*78, 79, 80*). The whole population will be followed for 10 years.

Of the 10,000 men randomized to the intervention group, 7,455 (or 75 percent) took part in the entry examination; approximately 65 percent were smokers (*78*). There are no indications in the scientific reports that investigations were implemented to determine whether there were any differences in individuals who participated when compared with those who did not come for screening. All men who smoked 15 or more g of tobacco per day (equivalent to 15 cigarettes or 3 cigars) were invited to an antismoking clinic (*78, 79*). Only 2.7 percent of the men screened smoked 25 or more cigarettes per day (*79*). Hypertension and hypercholesterolemia were given intervention priority so that men with elevated blood pressure or cholesterol would be referred for treatment to the relevant clinic and the clinic physician would also provide antismoking advice. The smokers of

more than 15 cigarettes per day were eventually sent to the special smoking clinic. The smoking clinic included about five small group sessions run by a physician and a psychologist (*79*). Very occasionally, men had an individualized session. All smokers, regardless of number of cigarettes smoked, were sent information about smoking and cessation and followup letters at 3, 5, and 12 months.

Objective measures of smoking were not used in this trial. The immediate rate of smoking cessation among the smokers referred to the antismoking clinic was 35 percent. (There is no indication whether this is for all smokers or just for those who attended.) After 3 months this rate fell to 23 percent. At the 4-year rescreening visit, it was reported that there was no significant difference in reported smoking cessation between the intervention and the control groups (*78*) (Table 2). A table presented in a paper reporting the trial results shows cessation rates of 31 and 26 percent at 4 years for the intervention and control groups, respectively (*78*), but upon which smokers these results are based is not indicated; thus, interpretation is difficult.

The Oslo (Norway) Study

The Oslo study (*16, 17, 18*), a 5-year randomized clinical trial, was designed to determine whether the lowering of serum lipids and cessation of cigarette smoking in middle-aged men would lower the incidence of CHD. Of the 16,202 volunteers screened, 40 to 49 years old, 1,232 healthy men free of overt cardiac and other chronic diseases but at high risk for CHD were randomized to an intervention (I) group (n =604) or to a control (C) group (n =628) (Table 1). All of the men at entry were normotensive with systolic blood pressures less than 150 mm Hg; had serum cholesterol levels of 290 to 380 mg/dl; and were in the upper quartile of CHD risk based on smoking and elevated serum cholesterol. Eighty percent were smokers. The two groups were very comparable on all risk factors, with a mean age of approximately 45 and the mean number of cigarettes smoked daily at 12.5 and 13 for intervention group and control group men, respectively (*16, 17*).

The smoking intervention program for the intervention group started immediately after randomization when each of the smokers met with Hjermann for 10 to 15 minutes and were informed about the risk factors and strongly advised to stop smoking all forms of tobacco. Special emphasis was placed on the synergistic effect of smoking and hyperlipidemia. Participants and their wives then attended a group session of 30 to 40 persons, where intervention included motivating the wives to aid their husbands in changing their smoking and eating habits. Half way through the trial, those men who continued to smoke were invited to attend in one group a "5-day smoking cessation program" (*16*).

The intervention group had followup examinations at the center every 6 months. These examinations took 20 to 30 minutes and included a physical examination aimed at cardiovascular symptoms, a resting ECG, and questions about smoking and dietary habits (*16, 17*). The control group returned for a similar examination annually. At the 5-year examination, followup was excellent, with only 1 percent of the men who were alive refusing to attend.

Self-reported smoking behavior at 3 years produced a cessation rate of 29 percent in the intervention group and 13 percent in the control group (*16*), a difference of 16 percent. Objective measures were not made at this point. Pipe smokers were included as smokers, one pack of pipe tobacco per week equaling seven cigarettes per day. Self-reported smoking behavior at 5 years indicated a 31 percent cessation rate in the intervention group and 18 percent cessation in the control group, producing a difference of 13 percent. Cessation of all tobacco smoking was 25 percent by self-report at year 5 in the intervention group and 1 percent in the control group (*16*). Although serum thiocyanate (SCN) was determined at the end of the trial as a validation of self-reported smoking, the corrected rates have not been reported. The investigators have noted that when serum SCN is used, the difference in cessation between the intervention group and the control group becomes smaller and there is a greater discrepancy between reported and corrected rates in the intervention group (*16*).

When smoking behavior is stratified, it can be noted that about 10 percent of the men at baseline both in the intervention group and in the control group were light smokers (one to nine cigarettes per day). This increased to about 30 percent in the intervention group by the end of trial. An increase in this group of light smokers was accompanied by a decrease in the group with heavier levels of smoking. This reported reduction in smoking did not occur in the control group. Most of the cessation in the control group occurred in the 10 to 19 cigarettes per day group and not in the lighter or heavier smokers (*16, 17*).

The percentage of nonsmokers continued to increase steadily in the control group over the duration of the trial, but the greatest increase in the intervention group occurred in the first year, with slight increases through year 4 and a slight decline in year 5; thus, a decrease occurred in the differences between the intervention and control groups during the fifth year (*16*). The number of cigarettes smoked per day decreased from 13 in both groups to about 7 in the intervention group and 11 in the control group, resulting in an almost 50 percent reported decrease in smoking in the intervention group (*17*).

The Multiple Risk Factor Intervention Trial (MRFIT)

The Multiple Risk Factor Intervention Trial was a randomized clinical prevention trial followed for an average of 7 years, designed to test the effect of a multifactor intervention program on coronary heart disease (CHD) mortality and morbidity (*19, 43*). There were 12,866 high-risk men, 35 to 57 years of age distributed among 22 clinical centers. They were randomly assigned either to a special intervention (SI) group that received treatment for hypertension, cigarette smoking, and elevated blood cholesterol levels or to a usual care (UC) group that received their usual health care in the community (Table 1). Persons were designated "at increased risk" if their levels of the three risk factors were sufficiently high at a first screening visit to place them in the upper 10 to 15 percent[1] of a risk score distribution based on data from the Framingham heart study.

Eligibility was determined at three successive screening visits. Men were excluded from the trial on the basis of low risk, history of certain diseases, among which were CHD and diabetes mellitus requiring medication, expected geographic mobility, a serum cholesterol level of 350 mg/dl or higher, or a diastolic blood pressure of 115 mm Hg or higher. Randomization resulted in an SI group with 6,428 participants and a UC group with 6,438 participants. There was excellent agreement in prerandomization levels of numerous risk factors and risk-factor-related variables (*19, 43, 49*), with a mean age of approximately 46 years and a mean number of 21 cigarettes smoked per day. The 64 percent of the participants who were smokers smoked an average of 34 cigarettes per day (*19, 49*). The proportion of men who were smokers decreased markedly as the age of the participants increased (*19*).

Since smokers were defined by their cigarette smoking habits, an individual who smoked only pipes and/or cigars or cigarillos at baseline but not cigarettes was not included in this group. Approximately 9 percent of the MRFIT participants smoked only pipes and/or cigars or cigarillos at baseline. Classification of this group as nonsmokers was in accord with the lack of substantial evidence linking this type of smoking with coronary artery disease.

Intervention for smoking cessation began after randomization at the third screening visit, when the smoker met with a physician who noted the effects of smoking on the cardiovascular and respiratory systems and strongly advised him to stop smoking. At this time the smoker also met with a "smoking specialist" who discussed the smoking intervention program with him and invited him to attend the intensive intervention group (*19*). Ninety-four percent agreed to join the group program, and 6 percent of the men elected to be seen individually. Each group included about 10 men and met for 10

[1]The percentage of risk was changed from the upper 15 percent to the upper 10 percent almost midway through screening. This change occurred in order to increase the power of the trial (*19*).

sessions. The men were encouraged to bring their spouses or friends to the series of weekly group discussions, which were intensive efforts to intervene in the three risk factors (*19, 48*). The smoking intervention program included a broad spectrum of educational, cognitive, and behavioral approaches for cigarette smoking cessation; no special effort was made to alter the smoking habits of persons smoking only pipes or cigars. Uniformity of content and structure was sought by the use of common protocols and educational material (*19, 48, 49*).

After the initial intensive intervention phase, individual counseling planned and executed by an intervention team became the general approach. Behavioral scientists often headed the intervention team, which also included nutritionists, nurses, physicians, and health counselors (*19, 49*). The smoking cessation program following the termination of the integrated intervention group was either a "maintenance program," directed at participants who had successfully quit cigarette smoking, or an "extended intervention program," directed at those who continued to smoke cigarettes or had stopped and recidivated. The key item in both the maintenance and the extended intervention components was a specified minimum contacts schedule. The maintenance program was based on a series of scheduled contacts between staff and participant, with the frequency of contacts decreasing over time as the participant continued to remain a nonsmoker. Participants who maintained their non-cigarette-smoking status were eventually seen by the smoking specialist at regular 4-month followup visits only.

Although similar methods, materials and protocols for schedules of contact and suggested sequencing of methods were used for smokers in the extended intervention phase, an individualized approach took into account individual needs and differences. Thus, although uniformity of content and structure was sought by the use of common protocols, methods, and educational materials, a single step-by-step procedure could not be used for smokers in this phase of intervention. It was not the goal of this study to treat all smokers alike; rather it was intended to produce the optimal treatment effect.

On or about each anniversary of randomization, participants in both the SI and the UC groups returned for assessment of risk factor levels, status on physical examination, laboratory studies, and morbidity status (*19, 43, 48, 49*). UC participants visited the clinical center once a year, and the results of the examinations were sent to their usual source of medical care. The missed-visit rates (the number of men alive at the time of the specified annual visit who did not attend, divided by the number of men randomized) were 4.5 percent for SI and 5.2 percent for UC men at 12 months; these increased only slightly each year and, although somewhat higher for

the UC group at each visit, remained below 10 percent through 6 years for both groups (*43*).

Serum thiocyanate (SCN) and carbon monoxide (CO) levels provided objective measures and a check on the validity of self-reported smoking. MRFIT used a multiple regression model, which takes factors affecting SCN (e.g., use of diuretics, pipes, or cigars) into account in order to "adjust" the reported data on cessation (*46*). Cessation rates that have been reported from MRFIT (*19, 48, 49*) therefore include both self-report and SCN-adjusted rates. At year 6, 43 percent of the SI smokers were reporting cessation, and 25 percent of the UC noted that they were not smoking (Table 2) (*48*). These rates include all baseline cigarette smokers so that individuals who did not attend the sixth annual visit were included at their baseline levels of smoking. When these rates are adjusted for SCN levels, they are 42 percent and 24 percent for SI and UC smokers, respectively, producing a statistically significant difference ($p < 0.01$) between SI and UC of 17 percent. Significantly more cessation occurred among lighter smokers in both treatment groups than among heavier smokers.

The reported cessation rate for SI smokers was relatively stable from year 1 to year 4—about 40 percent—and then increased in years 5 and 6 to 41 percent and 43 percent, respectively; cessation rates for UC smokers increased in a linear fashion from year 1 (about 13 percent) to year 6 (25 percent). Thus the SI–UC difference in reported and adjusted rates decreased each year, although always remaining significant. Similar to the Oslo study findings (*16*), there were greater discrepancies between reported and adjusted rates for SI smokers than for UC smokers early in the trial, although by the sixth year there was little discrepancy in either group. In year 3, the reported cessation rates were 40 and 16 percent for SI and UC smokers, respectively, and the adjusted rates were 35 and 15 percent (*48*).

Cohort analyses revealed that 26 percent of *all* SI smokers and 6 percent of *all* UC smokers stopped at year 1 and continued to report cessation through year 6 (*48*). That is, the 43 percent of the baseline SI smokers who reported cessation at year 6 included the 26 percent of the baseline smokers (or 60 percent of those smokers who initially stopped) who continued to report cessation each year and the 17 percent who had stopped later in the trial at years 2 through 5 or had recidivated and then stopped again. At year 2, 6.9 percent of baseline smokers were new stoppers. The rate of new reported cessation ranged from 3.3 to 4.7 percent at years 3 through 6. Similarly, the 25 percent reported cessation rate at 6 years for the baseline UC smokers include the almost 7 percent of the baseline smokers who continued to report cessation each year to year 6 and the 19 percent of the baseline UC smokers who had stopped later in

the trial at years 2 to 6 or had stopped earlier, then recidivated and stopped again. At year 2, 7.5 percent of baseline UC smokers reported new cessation. The rate of new cessation reported at years 3 through 6 was 4.2 to 4.8 percent.

Among smokers who stopped early in the trial (i.e., the early abstainers), the SI smokers had significantly less recidivism than did the UC, but among the late abstainers, the UC participants maintained their nonsmoking status somewhat better than did the SI cohort. The latter finding may reflect the differences in the remaining pool of smokers at the end of the first year of the program, with the smaller group of remaining SI smokers being those who were more recalcitrant and who would recidivate more readily. The data indicate that regardless of the conditions surrounding cessation (i.e., amount smoked, time from entry into the study at which cessation occurred, assignment to either the SI or UC group), the recidivism rates for the second and third year after cessation are much lower than for the first year (*49*).

Although the primary objective of the MRFIT smoking intervention program was total cessation, a program for dosage reduction was extended to smokers who had not been successful in their cessation attempts (*19*). It provided the trial an opportunity to continue working with participants who stated that they did not want to stop smoking completely. Reduction data that were reported through 4 years of the trial indicate that participants in the SI group who did not quit smoking reported reducing their cigarette smoking by approximately 10 cigarettes per day at year 1, smoking about three-quarters of their baseline rate (*19, 49*). This reduction continued to be reported through 4 years, but was not accompanied by a marked decrease in SCN levels. Since SCN levels can be utilized as a correlate of cigarette smoke exposure, there are at least two possible explanations of this finding. First, underreporting of cigarette consumption was occurring among continuing smokers. Second, smokers compensated for reductions in the number of cigarettes smoked, increasing the intensity of smoking by modifying the topography of puffing (*15*).

The Stanford Three-Community Study

From 1972 to 1975, the Stanford Heart Disease Prevention Program (SHDPP) conducted the Stanford Three-Community study, a field study in three comparable Northern California communities (*13, 14, 36, 41*). The noted objective of this communitywide health education project was to develop successful methods for reducing cardiovascular risk for the adult population at large that would be generally applicable within communities, hoping to demonstrate that it was indeed possible to reduce risk in this way (*36, 41*). In order to demonstrate that a community-based health education program

can decrease the risk of CHD, the program compared changes in risk behaviors and in risk factors (smoking, increased serum cholesterol, and hypertension) for subjects in two communities, using two different approaches to intervention, and in a third community, used as a no-intervention control.

To assess the effects of interventions on risk factor knowledge and behavior change, baseline and three annual followup surveys (medical examination and interview) were conducted for a random sample of approximately 500 men and women, aged 35 to 59, in each of three intervention groups (one community had two intervention groups) and in the control group (*36, 41, 44*). These exams took about 40 minutes each. High risk samples of individuals who were in the top quartile of risk at baseline were selected from these groups for further study (*41*). The male to female ratios in these high risk samples of individuals ranged from 0.97 to 1.36 (*41*).

One community, Gilroy, received a mass media program only; in a second community, Watsonville, a media approach was used, and in addition, intensive face-to-face intervention was provided for a randomized two-thirds of the participants who were in the top quartile of risk for CHD. A third community, Tracy, was selected as a no-treatment control community because it is geographically remote from the other two and does not have the media systems they share (*36, 41*) (Table 1). Followup at all three annual examinations was between 58 and 68 percent for each of the four groups, with the highest nonattendance occurring in the media plus face-to-face intervention groups (*14, 36, 41*). Of the high risk subjects, 59 to 66 percent of those subjects seen at baseline in three communities attended all three annual surveys, with the greatest nonattendance again in the face-to-face intervention group (*41*).

The media campaign consisted of spots on radio and television, newspaper columns, and mailings of different materials (*44*). The intensive instruction, or face-to-face counseling, took the form of group meetings or at-home instruction, whichever the participant preferred. The group, usually 12 to 15 participants, met in local church rooms for 10 weekly sessions and then twice a month for the first year. In many respects the intensive face-to-face intervention for the Stanford study is very similar to the MRFIT intensive intervention. Of the 169 subjects identified as being at high risk in Watsonville, 113 were randomized to treatment. Of these, 107 started treatment, and a cohort of 77 continued until the second annual examination. During the third year, little intervention took place.

Plasma thiocyanate (SCN) concentrations were determined at each annual survey to help distinguish smokers from nonsmokers. A concentration of greater than 100 μmol/liter was chosen to indicate possible inaccurate reporting (*41*). The investigators reported that

SCN measurement indicated that about 4 percent of those reporting abstinence "may have given false reports" (*14*), but SCN data were not integrated with the reported cessation rates (*24*). Therefore, the reported smoking behavior change results that follow have not been adjusted with SCN findings. The reported findings (*36, 41*) are also based only on those individuals attending followup surveys; dropouts and refusals are not an integral part of the analyses. Cessation results have been reported for high risk participants only.

For those individuals who attended all followup visits in the Watsonville intensive instruction group, a 50 percent cessation rate was reported (*41*) (Table 2). This rate becomes 32 percent when the 13 dropouts are included. Significantly fewer subjects stopped smoking in the Watsonville media-only group than did in the Tracy control community. In fact, no smokers who attended the 3-year followup visit in the Watsonville media-only group reported cessation, while 14.9 percent of the control group who attended the visit reported cessation. In the Gilroy media-only group, 11.3 percent reported cessation (*41*). For the cohort of individuals who attended all survey visits there was a steady increase in the number of smokers reporting cessation each year in the Watsonville face-to-face intervention group. This appeared to be true also for the control group. *No* cessation in the Watsonville media-only group was noted during any survey.

With regard to reduction in number of cigarettes smoked, there was a reported reduction of 51.6 percent for the smokers in the intensive instruction group who attended all three surveys (*41*). Data are not provided for the group of nonattendees. More reduction was reported in the control group (21 percent) than in the two media-only groups (10 and 11.8 percent, respectively).

Deficiencies in the Clinical Trials

In this review, the objectives, smoking control methods, and smoking behavior change findings of the major large-scale preventive trials have been presented. As noted in the beginning of this section, because of their emphasis on experimental design, preventive trials provide a valuable opportunity for scientifically assessing the efficacy and outcomes of smoking intervention techniques with special populations. Although they have greatly added to the quality of the available smoking-behavior-change data and the methodology used to assess intervention techniques and outcomes, they too are beset with deficiencies in some important areas. The major deficiencies noted in the reviewed trials are the lack of objective data to verify self-reported outcomes, the use of cross-sectional analyses to the almost complete exclusion of cohort analyses, failure to provide sufficient information in scientific reports to allow adequate inter-

pretation of outcomes, and lack of evaluation of components of the intervention packages.

The use of objective data to verify self-reported data was missing in two of the trials: the London Civil Servants smoking trial and the Göteborg study. Although SCN was reported to have been measured in the Stanford study and in the Oslo study, the findings were not used to correct the reported data. Only one trial—MRFIT—measured and used objective data to adjust reported cessation rates. As observed in the discrepancies between reported and objectively measured cessation data for intervention group smokers in studies that have used objective data for verification (e.g., MRFIT and the Oslo study), self-reports that have not been verified need to be interpreted with caution: often pressures to stop smoking, perceived and real, are felt by participants in an intervention program, which may cause misreporting and inflated cessation rates. The same pressures may lead to underreporting of consumption levels among continuing smokers, a possible interpretation of the MRFIT data showing reduced reported smoking among nonstoppers but maintained high SCN levels. Because of differences in the samples studied and in the intervention methods used, it is difficult to extrapolate from a study that has used objective data to a study that has not used these data. The very use of biochemical verification techniques of which subjects are aware has been shown to lower deception rates (*11, 35*). Thus, although MRFIT found a discrepancy of about 6 to 9 percent between reported and SCN-adjustment cessation rates, depending at which point of followup the measurements were made (*46*), the possibility of a similar discrepancy in another study using a different intervention approach and making different demands on different populations of smokers cannot safely be suggested.

None of the trials, with the exception of MRFIT, reported cessation outcomes for cohorts of smokers; they used cross-sectional data almost exclusively. Therefore there is very little understanding of the actual degree of recidivism occurring each year in either the intervention groups or the control groups in these trials or of the rate of new cessation taking place in either of the groups. A program that obtains an outcome of 30 percent cessation at year 2 and includes a large proportion of individuals who have been cigarette free for the 2 years is perhaps fulfilling the needs of smoking control programs more successfully than a program that yields a 40 percent cessation rate at 3 years and includes a large group of smokers who have gone back and forth with regard to smoking cessation. As has been consistently noted in the smoking literature, stopping is not the major problem, it is stopping and staying stopped (*5, 20, 34*). Even the commonly cited relapse curves (*20*) use cross-sectional data and do not give the true picture of relapse. In order to judge the effectiveness of a program, in addition to knowing cessation rates it is

important to know whether any new cessation occurs as the program progresses or whether all of the smokers available for cessation made changes early in the program. Is there a group of recalcitrant smokers whom the program never reaches? For example, Ockene et al. (*48*) noted with their use of cohort data that although there were new stoppers in the SI group each year, approximately 27 percent of baseline cigarette smokers never reported cessation during the next 6 years of the trial. Thus the program never reached slightly more than one quarter of the smokers, a fact that would not be brought out by cross-sectional data. None of this information can be provided with cross-sectional data.

The 51 percent reported cessation in the London Civil Servants trial (*58*) is impressive on first look, especially given the seemingly less expensive intervention approach, when compared with studies such as the Stanford study and the MRFIT. A major difference for this trial when compared with the other trials in this section is that the London Civil Servants trial was a one-factor trial, that is, smoking, and the others were multifactorial trials. This difference is an important one when considering intervention outcomes. In year 3, the rate fell considerably, to 36 percent. How many of the 36 percent of the smokers who reported cessation at year 3 in the Civil Servants trial also reported not smoking cigarettes at year 1? It is possible for this rate to be made up of individuals who were, in fact, not part of the original 51 percent at year 1. This lack of cohort data coupled with a lack of objective data makes it difficult to adequately interpret the outcomes. The Göteborg study investigators noted that there was no significant difference at 4 years for the intervention group relative to the control group. Although the cessation rates may not be significantly different, there may be significant differences in the percentage of smokers who met with long-term success in each group; thus, there is a possibility that the program had an effect on long-term outcome without differentially affecting the prevalence of smokers.

The nonuse of cohort data is also part of a third deficiency in the preventive trial literature: a lack of adequate information in the scientific reports to permit proper interpretation of outcomes. Also included here is a lack of adequate definitions of terms or criteria. Investigators in the London Civil Servants study (*55, 60, 61*) noted that additional smoking intervention help was provided "if needed." Likewise, the Oslo study provided a "5-day smoking cessation program" halfway through the trial for those who "continued to smoke" (*16*). There are no indications in either case of specifically how smokers who received additional help were defined, what percentage in fact needed it, what types of intervention were included in these programs, or what the outcomes of these specific programs were.

The lack of important data in the reports of some of the trials is yet another concern. In the Stanford study, 3-year cessation rates for each study group are provided for individuals who attended the visit, but rates that include nonattendees are not given for each community. A rate of 11.8 percent for the control community of Tracy does not give the full story. Likewise, the investigators in the Göteborg study provided a control group in which only 2 percent were initially screened, but all were assessed at 4 years (*78, 79, 80*). Comparison of 4-year data for the control group participants who were screened at baseline with those not screened would also have been useful, as a major problem noted for some of the trials is the possible intervention effect of screening. The Göteborg study could provide a valuable opportunity to investigate this possible intervention effect.

Another deficiency noted in the trials is the lack of evaluation of parts of the intervention packages. Most of the trials used approaches that combined many different behavioral, educational, and medical interventions, but were not able to note which components were most effective among all of the approaches. The data available at present tell us only the effects of the total intervention. The total package may have many components that can be delivered in different intensities or sequences to different subgroups of the target population (*24*). It is not possible to estimate the outcome of some changes in the total package, as there are too many confounding variables that prevent procurement of secure inferences with regard to the additive or interactive effectiveness of the individual components (*24*). Sorting out the effectiveness of single stages or elements in treatment packages has been a particularly complex area of research, with results indicating that simpler models can be superior (*30*). Also lacking are adequate studies designed to determine which subgroups of smokers benefit from certain interventions and which smokers respond poorly to these interventions (*47, 50*). Some persons may not need as intensive and expensive an intervention as used in the Stanford study and MRFIT and may do well with approaches similar to the less expensive and intensive approaches of the London Civil Servants study or the Oslo study or with less intervention. Trials testing differential intervention effects for subgroups of smokers would be able to provide valuable information.

Comparison of Clinical Trial Outcomes

Although deficiencies are present in the clinical trials, there are also many advances that these trials have made in smoking intervention studies. Each trial provided randomized control and intervention groups, long-term followup of at least 3 years, and standardized points of followup. The long-term followup of control and intervention groups provides some valuable data with regard to the process of smoking behavior change, although interpretation of

these data remains difficult because of the deficiencies as well as some of the differences inherent in the trials. In spite of these deficiencies and differences there remains much that we can learn from the trials reviewed above. The major points will be summarized in this section.

As noted in Table 2, the 3-year reported outcomes for all of these trials (except for the Göteborg study) showed a significant difference between the intervention groups and the control groups. The Göteborg study did not have 3-year data available, and the 4-year data showed no significant difference in cessation between the control and the intervention groups. The control groups in the trials where sufficient data are available (i.e., London Civil Servants study, the MRFIT, and the Oslo study) generally showed a steady increase in cessation as the trial progressed. In each of these studies there was a yearly examination for the control group smokers, raising the possibility of an intervention effect. In spite of the steady yearly increase of control group cessation rates in the trials, the MRFIT cohort data demonstrated that a significantly smaller percent of the control group smokers reporting cessation each year were long-term stoppers compared with the intervention group participants (*48*). Although cessation occurred among nonintervention smokers, it was probably not as well maintained as among the intervention group smokers. Because of the lack of cohort data, this issue cannot be reasonably addressed for the trials presented.

The range of cessation rates among the control groups at 3 years is 13 to 16 percent (except for the Göteborg study, which will be discussed below), with the highest rate recorded for the MRFIT. The London Civil Servants study provided an annual examination for the control group, but did not inform the participants of their high risk status. This latter point does not seem to have lessened the effect on cessation in the comparison group. On the contrary, the nonattendance rate for the control group in the London study was high—19 percent at year 3—which may in fact have decreased the cessation rate, since nonattendees were included as smokers.

The Göteborg study control group is unusual, with a possible cessation rate of 26 percent at 4 years. As noted, it is difficult to discern the rate from the investigators' scientific report. (Three-year rates were not reported.) Although the rate is slightly higher than what might possibly be expected at 4 years from the other control groups, it might be anticipated that with the steady yearly increases observed in the other trials, they would also have higher 4-year rates. A cessation rate of 21 percent was reported for the MRFIT UC group at 4 years, and at the 6-year visit this rate was 26 percent (*48*).

Where yearly data are available (i.e., London Civil Servants, MRFIT, Stanford study), control groups increased their cessation rates about 2 or 3 percent each year, and during the first year,

reported rates were about 10 percent. The 2 or 3 percent cessation rate each year is not unlike what might be expected from smoking cessation in the general population of smokers who stop smoking on their own each year without intervention (*75*). The greater cessation rate for the control group relative to the general population of middle-aged men at year 1 suggests that factors related to the trials—identification as being at high risk, the screening process, and the yearly examinations that include questions about smoking and cardiovascular fitness–may have had an intervention effect (*49*). Also, illness in this high risk group may have led to cessation.

With regard to the possibility of the effect of being at high risk, the Göteborg population is the only non-high-risk population in the noted trials, and they exhibited a high control group cessation rate. Likewise, although the London Civil Servant smokers were at high risk, the control group smokers were not informed of this status. Therefore, the increased awareness of one's smoking behavior through examination and questionnaires may be enough to motivate some persons to stop smoking. The onset of disease is certainly another possible factor. More analyses of the data for the control group smokers, including their reasons for cessation, must be accomplished before the variables affecting cessation in these groups can be better understood.

The reported cessation rates for the intervention groups (Table 2) in the trials at 3 years range from 29 percent for the Oslo study to 40 percent for the MRFIT. (For the Stanford study, only the results for the WII group are used here for comparison, i.e., 32 percent reported cessation.) In many respects, the five trials reviewed are remarkably similar with regard to the samples studied. The smoking cessation results reported were for healthy middle-aged men at high risk for CHD, except for the Göteborg study, which involved all middle-aged men, and for the Stanford study, which included an almost equal number of men and women in the intensive intervention group. The mean ages were similar in three studies (45 to 47), and in the Göteborg study and the London Civil Servants study the mean ages were 51 and 53, respectively. The greatest number of cigarettes smoked was by the men in the MRFIT study who smoked an average of 21 cigarettes per day. (The data for the Göteborg study are not clear with regard to the average number of cigarettes smoked per day by the smokers.) The least intensive intervention for smoking and the least expensive approach seemed to occur in the London Civil Servants smoking trial and the Oslo study, both of which used short initial visits with physicians and then one to three followup visits either individually (London study) or in a group (Oslo study). The fewest intervention visits were noted for the Oslo group. Both of these studies noted the use of additional intervention when necessary, but what this means or how much additional intervention was

provided is not specified. The Stanford study and the MRFIT seemed to provide the most intensive intervention, with at least 10 weekly group sessions and more if necessary. The smoking intervention program in the Göteborg study—small group sessions—falls between the two levels of intervention. In addition to the group sessions, the Göteborg study provided nicotine chewing gum at session two.

Each of the trials provided some continued contact, at least every 6 months and generally more often, for the intervention group smokers during the first 2 years of the trials. It appears as though the least maintenance contact may have been provided in the London Civil Servants study, although this is not entirely clear from the reports. Hypothetically, the more continued maintenance and intervention contacts provided, the greater the likelihood of new cessation and maintenance of cessation occurring. This possibility has been tested only for the MRFIT, since as noted previously, only cross-sectional data were available for the other studies. New cessation continued to occur in MRFIT each year at the rate of about 3 to 6 percent, and by the sixth year about two-thirds of the smokers who stopped initially continued to maintain cessation. Relative to past reports, this maintenance rate is indeed very promising, and it would be useful to know the maintenance rates of trials that used a lesser frequency of contact. Because of the continued contact, it is difficult to assess whether the followup data are good indicators of the level at which intervention effects stabilize (*24*).

The outcomes in the Stanford study are puzzling. At the third annual examination, the control community of Tracy showed the same rate of smoking cessation as the media-only town of Gilroy and significantly more cessation than the media-only intervention group in Watsonville. Zero percent of the Watsonville media-only group reported cessation, but there was a steady increase in the control group each year to about 15 percent. These data provide no support for the possibility that an intensive media blitz has an impact on smoking cessation that is greater than the impact of "usual" community intervention. Perhaps there is a "saturation point" with regard to the effectiveness of increased awareness, which when reached requires intervention to be at an intensive individual level before the next level of smokers can be affected. Albeit, a demonstrated intervention effect that is less than what is observed spontaneously in the general population merits investigation.

The Oslo study has the lowest 3-year reported cessation rate for the intervention groups, 24 percent, and seemed to deliver the least intensive intervention among the trials; the MRFIT had the highest cessation rate at 3 years, 40 percent, and perhaps provided the most intensive intervention among the trials. The best outcome was attained with the most intensive and perhaps the most expensive approach of the MRFIT, which demonstrated the possibility of long-

term cigarette smoking cessation with large numbers of people. Whether the intensive approach is cost effective must be evaluated. Similarly, as noted previously, it is important to determine whether there are certain groups of smokers who may not need intensive intervention and others who may require even more intensive work.

Even with the use of intensive intervention (Stanford study and MRFIT), a cross-sectional cessation rate of less than 50 percent was obtained. Is even more intensive intervention (or a different treatment package) desirable, or is this rate all that can be hoped for? Perhaps such intense interventions are not cost effective in terms of the outcome achieved, and much more attention should be devoted to self-help approaches.

Community Prevention Trials

The Heart Disease Prevention Project: World Health Organization European Collaborative Trials

The World Health Organization (WHO) European Collaborative Trials (*81*) were set up to evaluate the ability of a multifactoral intervention program to alter risk factors for CHD in industrial workers, aged 40 to 59, and the effect of such changes on CHD incidence and mortality. The allocation units were factories or other large occupational sites, thus permitting community health education as well as an individual approach. In most cases the program operated at the participants' workplace. The Collaborative Group included four centers: the United Kingdom, Belgium, Italy, and Poland. Although there was organizational diversity and each trial was essentially autonomous and self-sufficient, the experimental design was the same in each center with standardization of screening methods, intervention objectives, and end-point criteria (*81*). It was planned that each trial would run for about 5 years.

In each trial, factories or other occupational facilities were arranged in pairs and matched according to size, location, and type of industry, and then randomly allocated to an intervention or a control group. A central team visited each factory for screening. All men in the intervention factories between the ages of 40 and 59 and a random 10 percent of the men in the control factories were invited for a screening examination. The rest of the control men were not told of their participation in the trial, thus preventing a possible influence on risk factor change. The 10 percent of the controls who were initially screened were reexamined after 2 years. Random 5 percent samples of men in the intervention factories were reexamined annually in order to monitor risk factor changes. All survivors were examined at the termination of the trials (*81*).

Intervention was provided for hypercholesterolemia, cigarette smoking, sedentary activity, weight control, and hypertension. All of

the men in the intervention factories were exposed to mass intervention approaches such as posters, groups, films, and demonstrations and received a report of their results along with printed advice for change. Their personal physicians also received copies of the reports. Individualized intervention consultations were provided for the 10 to 20 percent of the men who, as a result of screening, were assessed to be at the "highest risk for CHD." The intervention approach used in this trial was similar in some respects to that of the Stanford study insofar as both used a combination of face-to-face and mass media techniques.

Information specific for the United Kingdom and Belgium trials and their results is presented below. The Rome and Warsaw trials have not yet reported their results.

United Kingdom Heart Disease Prevention Project

Recruitment for the heart disease prevention project in the United Kingdom occurred between 1971 and 1973. Twenty-four large industrial groups, generally factories, employing a total of 18,210 men, were recruited and paired (*62*). One of each pair was allocated to the intervention group (9,734 subjects) and to the control group (8,476 subjects). Intervention began with the acceptance of screening by 86 percent of the men aged 40 to 59. A cutoff risk factor score was determined within each intervention factory, such that it was exceeded by 12 to 15 percent of the examined men who were at "high risk" for CHD. Differences between factories in the mean levels of risk factors were slight (*62, 81*), with a mean age of approximately 50 for both groups and a mean number of cigarettes smoked of approximately 8 cigarettes per day for all men and 14.3 cigarettes per day for the high risk men (*62, 81*) (Table 3).

Intervention for all of the smokers in the intervention factories was initiated at the screening examination, when they were asked if they would like to stop smoking (*62*). The 40 percent who were interested were sent a letter of encouragement, smoking record cards that they were asked to return after 3 weeks, and a booklet with smoking cessation advice. All screened participants were sent general information on risk factors, and the mass health education intervention included posters, evening meetings to which spouses were invited, films, talks, and question and answer sessions. Because of the generally poor response to the community intervention in the first 2 years, more personal contact was added for men whose risk scores came close to the high risk scores. Annual examinations were also used to give personal advice on smoking and diet. In the third year, antismoking clinics for all smokers were held by a nurse. The high risk men were recalled after screening by the company physician, who advised and treated them individually. There was an

TABLE 3.—Population, randomization, and baseline smoking data for three major community prevention trials

Community trial (duration)	Population	Randomization methods/ study groups	Baseline smoking data
WHO European Collaborative Trial: United Kingdom *(62, 81)* (5 years) (screening 1971–1972)	18,210 factory workers Aged 40–59 24 large industrial groups (paired)	Factories paired for similarities Random allocation of one in each pair to intervention or to no intervention Intervention group (IG) = 9,734 males Control group (CG) = 8,476 males	$\bar{X}$ cigs for all participants = 8 $\bar{X}$ cigs for high risk males = 14.3
WHO European Collaborative Trial: Belgium *(8, 26, 27)* (5 years) (screening 1972–1974)	16,222 factory workers Aged 40–59 30 industrial groups (paired)	Same randomization as above Intervention group (IG) = 7,398 males Control group (CG) = 8,240 males	$\bar{X}$ cigs not noted

TABLE 3.—Continued.

Community trial (duration)	Population	Randomization methods/ study groups	Baseline smoking data
North Karelia (Finland) Project (*53, 54, 63, 64, 65*) (5 years) (screening 1972–1977)	Residents of North Karelia (Intervention community = IC) Residents of Kuopio (Control community = CC) Surveyed residents aged 25–59 at start of study	No randomization North Karelia had a high CVD rate and intervention was indicated Community similar to North Karelia was matched as a control Random 6.6% sample of population aged 25–59 in each community surveyed in 1972 Random 6.6% sample (independent of 1st sample) surveyed at study end in 1977 Over 10,000 subjects studied each time	IC: 50.2% males smoked 11.7% females smoked CC: 50.9% males smoked 13.1% females smoked X cigs (CC) = 8.9 for all males X cigs (IC) = 9.9 for all males X cigs (IC) = 19 for all smokers

average of about four 15-minute visits per high risk smoker during the first year (*62*).

Changes in risk factors for intervention were assessed each year for a new 5 percent random sample of all entrants. At year 5, half of all the men who had not been previously assessed were called, and at year 6, assessment was accomplished for the other half still employed. Followup of high risk men occurred at either the second or fourth year. A random 10 percent of the men in the control group were invited to an examination at entry and again at 2 years and at 4 years. The results for the intervention group were corrected for corresponding changes in the control group (*62*). Followup visits in all groups ranged from 86 to 94 percent of those invited.

Objective measures were not used to validate self-reported smoking behavior. High risk men reported the best changes in smoking levels, with a decrease in number of cigarettes per day from approximately 13 at entry to about 9 at the final examination, a 29 percent decrease. No decrease was noted for the control group; thus, the corrected estimate for the effect of intervention at the final examination was also minus 29 percent (*62*). There was a net reduction in number of cigarettes smoked of 19 percent for all smokers and of 16 percent when high risk smokers were removed.

At the end of the trial, a 12 percent cessation rate for the high risk men in the intervention group was reported, but no change was reported in the control group (Table 4). About 9 percent of all of the intervention smokers reported cessation by the end of the trial, which is about 7 percent if high risk smokers are excluded (*62*). These differences are statistically significant ($p \leq 0.001$). A comparison of risk factor levels at the final examination between the 90 percent of the control group men who had no contact with the trial before the examination and the remaining 10 percent who had been examined showed almost identical results for smoking (*62*).

The Belgium Heart Disease Prevention Project

After a preliminary feasibility study in 1971–1972 for the Belgium trial, initial examination for the main trial began in 1972 and terminated in April 1974 (*81*). The trial paired 30 Belgian industries, with 1 member of each pair randomized to the intervention and 1 to the control group (*8, 26, 27*). Out of 19,390 male workers in the age group of 40 to 59, 83.7 percent agreed to be screened, yielding 7,398 men in the intervention group and 8,821 men in the control group. There are no indications that investigations were implemented to determine whether there were differences between persons who were screened and a random sample of those who were not screened. Ten percent of the subjects in each occupational unit were randomly selected for an examination similar to that of the intervention group; the other 90 percent had a resting electrocardiogram (*8, 26, 27*). The

TABLE 4.—Intervention, followup, and cessation results for three major community prevention trials

Community trial	Intervention	Control group contact	Followup	Reported cessation rates/ (objective measures)		
				Treated	Control	Time
WHO European Collaborative Trial: United Kingdom (62)	Mass media intervention for all factory workers Antismoking clinics for all smokers High risk smokers (top 10–15% risk) offered individual treatment (four 15 min sessions in year 1 with company physician)	Random 10% sample invited for screening The rest of control males not told of their participation in the trial	Random 5% IG examined yearly All survivors examined at end of trial Same random 10% CG screened, reexamined at 2 years	12%[1] (high risk smokers) 9% (all smokers) 7% (non-high-risk smokers) (no objective measures used)	(no change)	5 yrs
WHO European Collaborative Trial: Belgium (62)	Mass media intervention for all factory workers High risk smokers (top 21% risk) offered counseling and examination by project physicians twice per year	Random 10% invited for screening Other 90% had resting ECG only	Random 5% IG examined yearly All survivors examined at end of trial	18.7%[2] (high risk smokers) 12.5% (all smokers) (no objective measures used)	12.2% (high risk smokers) 12.6% (all smokers)	2 yrs

TABLE 4.—Continued.

Community trial	Intervention	Control group contact	Followup	Reported cessation rates/ (objective measures)		
North Karelia (Finland) Project (*52, 53, 63*)	Comprehensive "community action" program against risk factors All forms of media used Special groups set up as needed	6.6% random sample examined at baseline and 5 years	Random 6.6% of each community surveyed and examined in 1977 Results compared to assess RF change	17%[3] (male smokers)	15% (male smokers) (SCN drawn for random subsamples) (Correlations reported, but adjustments not made)	5 yrs

[1] $P \leq 0.01$.
[2] $P \leq 0.05$.
[3] Not significant.

intervention subjects in the top 21 percent of the risk score distribution were placed in the high risk group (n=1,601).

All smokers in the intervention factories received the mass media approach previously noted for the WHO trials, and all family and factory physicians received regular information about the participants' risk factors and took part in intervention (*8, 26, 27*). Twice a year, high risk subjects were individually counseled and examined by two project physicians (*8, 26, 27*) (Table 3).

Reports of the smoking results for this trial have included comparisons of the results for the 5 percent random sample in the intervention group with the results for the 10 percent random sample of the control group at 2-year followup and comparisons of the results of the high risk subjects in the intervention group with the results of the high risk subjects selected from the 10 percent random sample of the control group screened at baseline (*9, 26, 27*).

Reported smoking rates have not been validated with objective measures. Among the high risk smokers, 18.7 percent in the intervention group and 12.2 percent in the control group reported cessation at 2 years, producing a statistically significant difference ($p \leq 0.05$). For the random samples there was no difference in reported cessation, with approximately 12.5 percent of the smokers reporting cessation in both groups (*26, 27*). Smoking cessation rates for the intervention group at 1 year was 12 percent and 8 percent for the high risk subjects and the random sample, respectively (*27*), indicating that cessation occurred gradually over the 2-year period.

The North Karelia (Finland) Project

The North Karelia project was carried out in Finland during 1972–1977 as a comprehensive community program to study the control of cardiovascular disease (CVD), with special emphasis on CHD, by reduction of the major alterable CHD risk factors (smoking, increased serum cholesterol, and hypertension (*52, 53, 54, 63, 64, 65*). The intervention area was the county of North Karelia in eastern Finland, which had the highest rates of CVD in that country. The county of Kuopio, also in eastern Finland, was selected as the control area because of its similarity to North Karelia.

Both in 1972 and in 1977 a representative random 6.6 percent sample of the population born between 1913 and 1947 (aged 25 to 59 in 1972 and 30 to 74 in 1977) was drawn from the two counties by using the national population register (*53, 54*). The samples in 1972 and in 1977 were independent of each other. Those persons surveyed were sent a letter explaining the study, a questionnaire assessing medical history, health behavior and attitudes, attempts to change health behavior, and stress and an invitation and date for a physical examination. Over 10,000 subjects were studied each time, with a participation rate of about 90 percent (*52, 53, 54, 63, 64, 65*).

The comprehensive "community action" program against risk factors was integrated into the health and social services of the county and was aimed at primary and secondary prevention, although primary prevention was emphasized. Public information was provided through newspapers, radio, leaflets, posters, health education meeetings, and campaigns at schools and places of work (*53*); new services were set up if needed, personnel were trained, and environmental changes (e.g., smoking restrictions) were implemented. The project team planned the activities, prepared the educational material, helped train personnel, and got the community into action (*54*). Smoking cessation group activities were available to those smokers who wanted them, on the basis of a 3-week model developed by the project (*63*). Approximately 55 percent of the smokers were willing to join the groups, and 71 percent of those who started completed the groups (*63*). Approximately 27 percent of those who started the group reported smoking cessation at 6 months.

The outcomes concerning changes in smoking are based on the comparison of data obtained in the baseline survey and in the 5-year terminal survey from the study community and the matched control community. The validity of the self-reports of smoking behavior was tested on a random subsample of subjects who were given a second interview about smoking by trained nurses unaware of the answers to the survey questionnaire (*53*). When classified by an interval of 5 or 10 cigarettes, the agreement between the two results was 93 and 97 percent, respectively. The agreement was 99 percent when classification was smoker or nonsmoker (*53*). Serum thiocyanate (SCN) determinations made during the termination interview provided further validation. Since it is not otherwise noted in the scientific reports, it is assumed that the results are based on self-report and are not corrected. Individuals who reported ever having smoked regularly or having smoked during the preceding month on an average of more than once a day were classified as smokers. The reported number of cigarettes, cigars, and pipes smoked per day was calculated as the amount smoked (*53*).

The prevalence of smoking in the study and in the control area for men was 50.2 and 59.9 percent, respectively, and for women 11.7 and 13.1 percent at the start of the study. At year 5, 17 percent of the baseline male smokers in North Karelia reported smoking cessation and 15 percent of the baseline male smokers in Kuopio reported cessation of smoking (*52, 53*) (Table 4). Thus, smoking had decreased considerably in both the control and the study groups, yielding a nonsignificant net reduction in North Karelia of 2.5 percent for the men and 6.1 percent for the women. With regard to amount smoked, North Karelian men smoked more than did the men in the control area in 1972 (9.9 versus 8.9 cigarettes per day), and both groups were smoking 8.1 cigarettes per day by the end of the study (*53*), producing

a significant net reduction among North Karelian men of 9.8 percent. The mean number of cigarettes smoked by smokers in North Karelia was 19 cigarettes per day, which remained stable during the study (*63*).

A small net reduction occurred in the prevalence of smoking because, even though considerable cessation was reported in North Karelia, smoking also decreased at a similar rate in Kuopio, the control area. The investigators noted several possible explanations for this decrease (*53*). There was an increase in interest in antismoking activities toward the end of the study period: the Finnish Parliament passed new antismoking legislation in 1976, and a new medical school opened in Kuopio in 1972. They also indicated on the basis of internal followup surveys that most of the reduction in smoking occurred at the beginning of intervention in North Karelia, after the first intensive public antismoking campaign, and that this lower level of smoking was maintained during the rest of the period (*39, 63*).

Deficiencies in the Community Preventive Trials

The major deficiencies in these community preventive trials are the same as those noted for the clinical trials; i.e., lack of objective data to verify self-reported outcomes, use of cross-sectional analyses to the almost complete exclusion of cohort analyses, failure to provide sufficient information in scientific reports to allow adequate interpretation of outcomes, and lack of evaluation of components of the intervention packages.

Objective data to verify self-reports were not used in the United Kingdom and the Belgium heart disease prevention projects, and although SCN was measured in the North Karelia study, it was not used to adjust the self-reported cessation data. Data for strata of smokers by age were presented for the North Karelia study (*74*), but not for cohorts of smokers by smoking-behavior-change categories. Longitudinal data for cohorts of smokers in the other two trials were not presented. The value of cohort data is illustrated by a statement made by the North Karelia investigators in which they noted that even though the smoking cessation rates were similar in North Karelia and Kuopio, most of the cessation in North Karelia occurred at the beginning of the project and was maintained (*63, 74*). This information was obtained by the use of followup surveys of samples of residents. It was hypothesized that most of the cessation for the comparison community may have occurred near the termination of the project when antismoking legislation and other changes had occurred there (*39, 63*). Cohort data for the comparison community or for subgroups are not available; thus, the hypothesis cannot be tested.

Use of the same subjects for baseline and termination surveys are likely to influence outcomes; therefore, the change may look better than it actually is (*53, 54, 63*). The use of a cohort design might therefore produce a net effect that is not totally a consequence of the intervention alone, but may also include the effect of the first survey as well as its interaction with the intervention (*63*). Thus, there is a possible need to examine independent cross-sectional population samples in the two areas under study at the start and termination of the project. This hypothesis is not supported by data from the North Karelia study, where cessation rates for 6.6 percent of the random sample of smokers in the baseline survey of the control community who were also included in the termination survey were similar to the rates for the rest of the smokers who were surveyed only at termination (*63*). Data from the United Kingdom heart disease prevention project (*62*) also failed to support the hypothesis of a possible intervention effect from screening.

Different components of intervention were not differentially evaluated within any of the community trials because of the community orientation of the projects. Thus, conclusions about the relative contributions of different programs, subprograms, or channels of action cannot be drawn (*39*).

Comparison of Community Trials Outcomes

As is noted in Table 4, the 2-year cessation data for both the Belgium and the United Kingdom WHO trials demonstrate that there were significant differences in reported cessation rates for the intensively intervened-with high risk smokers as compared with the smokers in the control factories, but there were no significant differences between the non-high-risk smokers in the intervention factories who received a media-only approach as compared with the non-high-risk smokers in the control factories. This outcome is similar to the previously noted finding in the Stanford study; i.e., media only had no more intervention impact than had no intervention. This lack of demonstrated impact for a media approach to smoking cessation in the Belgium study was in part due to the 12.5 percent cessation rate achieved by the control group. This occurrence of cessation in a control group is similar to that demonstrated in each of the clinical trials. Again, a saturation point may have been reached in groups in which there is already an increased level of awareness, and intensive intervention may be necessary if additional cessation is to be realized in the next level of smokers. It may also be, as previously noted, that although cessation occurred among the nonintervention smokers, the long-term maintenance rate among those in this group who stop smoking may be significantly different from the long-term maintenance rate for the intervention group

smokers. Because of the lack of cohort data, this issue cannot be addressed.

The range of cessation rates among the comparison groups for the three trials is large, 0 to 15 percent, with the lowest rate recorded for the United Kingdom group of the WHO collaborative study and the highest for the Belgium group of the same study. The 0 percent cessation rate for the control group in the United Kingdom trial is puzzling, as this is less than the spontaneous cessation rate observed in the general population. More in-depth analysis of the data for the 10 percent random sample of the control group who were screened at baseline and reexamined at 2 years is indicated. Different protocols for contact with the control group were used for the United Kingdom from those used for the Belgium groups. The most notable difference was that 90 percent of the United Kingdom control group were not told of their participation in the trial, but 90 percent of the Belgium group were told of their participation and had a resting ECG. An additional 10 percent were told of their participation and had complete physical examinations. It can be hypothesized that the use of an ECG may have had an intervention effect for the Belgium control group. The 15 percent rate for the North Karelia study was determined at 5 years. One might hypothesize that this rate would be lower at 2 years, the point at which the other two studies conducted followup.

The 5-year cessation rate for the United Kingdom collaborative trial is also low when compared with the 2-year rate for the Belgium collaborative trial, which utilized a similar protocol. A major difference for these two groups was that high risk smokers in the Belgium study received two examinations per year while those in the United Kingdom were given one. There was also a difference in the number of physician-intervention visits during year 1; two were used in the Belgium study and four were used in the United Kingdom trial. Perhaps the feedback provided by an examination has a greater intervention effect than a session with a physician intended for counseling only. It can also be hypothesized that cultural differences may have affected the differences in outcome between the two groups in the same trial.

In general, the use of community programs that used only a media approach did not produce a greater intervention effect than was observed in the comparison community. The incorporation of more intensive intervention in groups in addition to the media approach was necessary before significant differences could be realized. The same outcomes were observed in the Stanford study.

Conclusions

1. Smokers involved in intervention programs demonstrate higher smoking cessation rates than those in control groups.
2. In general, the success of smoking intervention programs is related to the amount of intervention provided.

References

(1) BARRETT, T.J., SACHS, L.B. Test of the classical conditioning explanation of covert sensitization. *Psychological Reports* 34(3): 1312–1314, June 1974.

(2) BENFARI, R.C. The Multiple Risk Factor Intervention Trial (MRFIT) III: The model for intervention. *Preventive Medicine* 10(4): 426–442, July 1981.

(3) BENFARI, R.C., McINTYRE, K., BENFARI, M.J.F., BALDWIN, A., OCKENE, J. The use of thiocyanate determination for indication of cigarette smoking status. *Evaluation Quarterly* 1(4): 629–638, November 1977.

(4) BENOWITZ, N.L., HALL, S.M., HERNING, R.I., JACOB, P. III, JONES, R.T., OSMAN, A.-L. Smokers of low-yield cigarettes do not consume less nicotine. *New England Journal of Medicine* 309(3): 139–142, July 21, 1983.

(5) BERNSTEIN, D.S. Modification of smoking behavior: An evaluative review. *Psychological Bulletin* 71(6): 418–440, June 1969.

(6) CHEN, T. *Smoking Behavioral Change and Its Correlates in a Selected Group of Middle-Aged Men.* Doctoral dissertation, Ohio State University, University Microfilms International, Ann Arbor, Michigan, Thesis number 71–7422, 1970.

(7) COLTON, T. *Statistics in Medicine.* Boston, Little, Brown and Company, 1974, 372 pp.

(8) DeBACKER, G., KORNITZER, M., THILLY, C., DEPOORTER, A.M. The Belgian multifactor preventive trial in CVD (I) design and methodology. *Hart Bulletin* 8(6): 143–146, December 1977.

(9) DerSIMONIAN, R., CHARETTE, L.J., McPEEK, B., MOSTELLER, F. Reporting on methods in clinical trials. *New England Journal of Medicine* 306(22): 1332–1337, June 3, 1982.

(10) DiCLEMENTE, C.C., PROCHASKA, J.O. Self-change and therapy change of smoking behavior: A comparison of processes of change in cessation and maintenance. *Addictive Behaviors* 7(2): 133–142, 1982.

(11) EVANS, R.I., HANSEN, W.B., MITTLEMARK, M.B. Increasing the validity of self-reports of smoking behavior in children. *Journal of Applied Psychology* 62(4): 521–523, April 1977.

(12) EVANS, D., LANE, D.S. Long-term outcome of smoking cessation workshops. *American Journal of Public Health* 70(7): 725–727, July 1980.

(13) FARQUHAR, J.W. The community-based model of life style intervention trials. *American Journal of Epidemiology* 108(2): 103–111, August 1978.

(14) FARQUHAR, J.W., WOOD, P.D., BREITROSE, H., HASKELL, W.L., MEYER, A.J., MacCOBY, N., ALEXANDER, J.K., BROWN, B.W., Jr., McALISTER, A.L., NASH, J.D., STERN, M.P. Community education for cardiovascular health. *Lancet* 1(8023): 1192–1195, June 4, 1977.

(15) GRITZ, E.R. Smoking behavior and tobacco abuse. In: Mello, N.K. (Editor). *Advances in Substance Abuse.* Volume 1. Greenwich, Connecticut, JAI Press, 1980, pp. 91–158.

(16) HJERMANN, I. Smoking and diet intervention in healthy coronary high risk men. Methods and 5-year follow-up of risk factors in a randomized trial. The Oslo study. *Journal of the Oslo Hospitals* 30(1): 3–17, January 1980.

(17) HJERMANN, I., VELVE BYRE, K., HOLME, I., LEREN, P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo study group of a randomized trial in healthy men. *Lancet* 2(8259): 1303–1310, December 12, 1981.

(18) HOLME, I., HELGELAND, A., HJERMANN, I., LEREN, P. The Oslo study: Social indicators, risk factors and mortality. In: Bostrom, H., Ljungstedt, N. (Editors). *Medical Aspects of Mortality Statistics.* Skandia International Symposia. Almquist and Wiksell International, Stockholm, Sweden, 1981, pp. 165–181.

(19) HUGHES, G.H., HYMOWITZ, N., OCKENE, J.K., SIMON, N., VOGT, T.M. The Multiple Risk Factor Intervention Trial (MRFIT). V. Intervention on smoking. *Preventive Medicine* 10(4): 476–500, July 1981.

(20) HUNT, W.A., BESPALEC, D.A. An evaluation of current methods of modifying smoking behavior. *Journal of Clinical Psychology* 30(4): 431–438, October 1973.

(21) JACOB, P., III, WILSON, M., BENOWITZ, N.L. Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. *Journal of Chromatography* 222(1): 61–70, January 2, 1981.

(22) JACOBS, M.A., SPILKEN, A.Z., NORMAN, M.M., WOHLBERG, G.W., KNAPP, P.H. Interaction of personality and treatment conditions associated with success in a smoking control program. *Psychosomatic Medicine* 33(6): 545–556, November-December 1971.

(23) KANZLER, M., ZEIDENBERG, P., JAFFE, J.H. Response of medical personnel to an on-site smoking cessation program. *Journal of Clinical Psychology* 32(3): 670–674, July 1976.

(24) KASL, S.V. Cardiovascular risk reduction in a community setting: Some comments. *Journal of Consulting and Clinical Psychology* 48(2): 143–149, April 1980.

(25) KEUTZER, C.S. Behavior modification of smoking: The experimental investigation of diverse techniques. *Behavior Research and Therapy* 6(2): 137–157, May 1968.

(26) KORNITZER, M., DeBACKER, G., DRAMAIX, M., THILLY, C. The Belgian Heart Disease Prevention Project: Modification of the coronary risk profile in an industrial population. *Circulation* 61(1): 18–25, January 1980.

(27) KORNITZER, M., DRAMAIX, M., KITTEL, F., DeBACKER, G. The Belgian Heart Disease Prevention Project: Changes in smoking habits after two years of intervention. *Preventive Medicine* 9(4): 496–503, July 1980.

(28) LANDO, H.A. A comparison of excessive and rapid smoking in the modification of chronic smoking behavior. *Journal of Consulting and Clinical Psychology* 43(3): 350–355, June 1975.

(29) LANDO, H.A. Measurement and technique innovations. An objective check upon self-reported smoking levels: A preliminary report. *Behavior Therapy* 6(4): 547–549, July 1975.

(30) LANDO, H.A., McGOVERN, P.G. Three-year data on a behavioral treatment for smoking: A follow-up note. *Addictive Behaviors* 7(2): 77–181, 1982.

(31) LANGONE, J.J., Van VUNAKIS, H., HILL, P. Quantitation of cotinine in sera of smokers. *Research Communications in Chemical Pathology and Pharmacology.* 10(1): 21–28, January 1975.

(32) LEVENBERG, S.B., WAGNER, M.K. Smoking cessation: Long-term irrelevance of mode of treatment. *Journal of Behavior Therapy and Experimental Psychiatry* 7(1): 93–95, March 1976.

(33) LEVENTHAL, H. Experimental studies of anti-smoking communications. In: Borgatta, E.F., Evans, R.R. (Editors). *Smoking, Health, and Behavior.* Chicago, Aldine Publishing, 1968, pp. 95–121.

(34) LICHTENSTEIN, E., DANAHER, B.G. Modification of smoking behavior: A critical analysis of theory, research, and practice. *Advances in Behavior Modification* 3: 79–132, 1976.

(35) LUEPKER, R.V., PECHACEK, T.F., MURRAY, D.M., JOHNSON, C.A., HUND, F., JACOBS, D.R. Saliva thiocyanate: A chemical indicator of cigarette smoking in adolescents. *American Journal of Public Health* 71(12): 1320–1324, December, 1981.

(36) MACCOBY, N., FARQUHAR, J.W., WOOD, P.D., ALEXANDER, J. Reducing the risk of cardiovascular disease: Effects of a community-based campaign on knowledge and behavior. *Journal of Community Health* 3(2): 100–114, Winter 1977.

(37) MARSTON, A.R., McFALL, R.M. Comparison of behavior modification approaches to smoking reduction. *Journal of Consulting and Clinical Psychology* 36(2): 153–162, April 1971.

(38) MATTSON, M., FURBERG, C.D., DUNBAR, J., SCHUCKER, B. Behavioral sciences in clinical trials: An overview. *Behavioral Medicine Update* 2(4): 6–10, Fall 1982.

(39) McALISTER, A., PUSKA, P., SALONEN, J.T., TUOMILEHTO, J., KOSKELA, K. Theory and action for health promotion: Illustrations from the North Karelia Project. *American Journal of Public Health* 72(1): 43–50, January 1982.

(40) McFALL, R.M. HAMMEN, C.L. Motivation, structure, and self-monitoring: Role of nonspecific factors in smoking reduction. *Journal of Consulting and Clinical Psychology* 37(1): 80–86, August 1971.

(41) MEYER, A.J., NASH, J.D., McALISTER, A.L., MACCOBY, N., FARQUHAR, J.W. Skills training in a cardiovascular health education campaign. *Journal of Consulting and Clinical Psychology* 48(2): 129–142, April 1980.

(42) MITTLEMARK, M.B. *Information on Imminent Versus Long Term Health Consequences: Impact on Children's Smoking Behavior, Intentions, and Knowledge.* Doctoral dissertation, University of Houston, University Microfilms International, Ann Arbor, Michigan, Thesis number 78–18238, May 1978, 166 pp.

(43) MULTIPLE RISK FACTOR INTERVENTION RESEARCH GROUP. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. *Journal of the American Medical Association* 248(12): 1465–1477, September 24, 1982.

(44) NASH, J.D., FARQUHAR, J.W. Applications of behavioral medicine to disease prevention in a total community setting: A review of the three community study. In: Ferguson, J.M., Taylor, C.B. (Editors). *The Comprehensive Handbook of Behavioral Medicine. Volume 3: Extended Applications and Issues.* Spectrum Publications, Jamaica, New York, 1980, pp. 313–335.

(45) NATIONAL INTERAGENCY COUNCIL ON SMOKING AND HEALTH. *Guidelines for Research on the Effectiveness of Smoking Cessation Programs. A Committee Report.* National Interagency Council on Smoking and Health, American Dental Association, Chicago, October 1974, 46 pp.

(46) NEATON, J.D., BROSTE, S., COHEN, L., FISHMAN, E.L., KJELSBERG, M.O., SHOENBERGER, J. The Multiple Risk Factor Intervention Trial (MRFIT). VII. A comparison of risk factor changes between the two study groups. *Preventive Medicine* 10(4): 519–543, July 1981.

(47) OCKENE, J.K. *A Study of the Psychosocial Factors Involved in Changing Smoking Behavior: Risk Factor Alteration in a Coronary Heart Disease Prevention Program.* Doctoral Thesis, Boston College, Department of Education, Boston. University Microfilms International, Ann Arbor, Michigan, Thesis number 79–22078, 1979, 286 pp.

(48) OCKENE, J.K., BROSTE, S., HYMOWITZ, N., HUGHES, G., LAUGER, G. For the MRFIT Research Group Paper presented at Council on Epidemiology, American Heart Association, San Diego, California, March 1983.

(49) OCKENE, J.K., HYMOWITZ, N., SEXTON, M., BROSTE, S.K. Comparison of patterns of smoking behavior change among smokers in the Multiple Risk Factor Intervention Trial (MRFIT). *Preventive Medicine* 11(6): 621–638, November 1982.

(*50*) OCKENE, J.K., NUTALL, R., BENFARI, R.C., HURWITZ, I., OCKENE, I.S. A psychosocial model of smoking cessation and maintenance of cessation. *Preventive Medicine* 10(5): 623–638, September 1981.

(*51*) PETTIGREW, A.R., FELL, G.S. Microdiffusion method for estimation of cyanide in whole blood and its application to the study of conversion of cyanide to thiocyanate. *Clinical Chemistry* 19(5): 466–471, 1973.

(*52*) PUSKA, P., KOSKELA, K., PAKARINEN, H., PUUMALAINEN, P., SOININEN, V., TUOMILEHTO, J. The North Karelia Project: A programme for community control of cardiovascular diseases. *Scandinavian Journal of Social Medicine* 4(2): 57–60, 1976.

(*53*) PUSKA, P., TUOMILEHTO, T., SALONEN, J., NEITTAANMAKI, L., MAKI, J., VIRTAMO, J., NISSINEN, A., KOSKELA, K., TAKALO, T. Changes in coronary risk factors during comprehensive five-year community programme to control cardiovascular diseases (North Karelia Project). *British Medical Journal* 2(6198): 1173–1178, November 10, 1979.

(*54*) PUSKA, P., VIENOLA, P., KOTTKE, T.E., SALONEN, J.T., NEITTAANMAKI, L. Health knowledge and community prevention of coronary heart disease. *International Journal of Health Education* 24(Supplement 2): 1–11, April-June 1981.

(*55*) REID, D.D., HAMILTON, P.J.S., KEEN, H., BRETT, G.Z., JARRETT, R.J., ROSE, G. Cardiorespiratory diseases and diabetes among middle-aged male civil servants. *Lancet* 1(7856): 469–473, March 23, 1974.

(*56*) RINGOLD, A., GOLDSMITH, J.R., HELWIG, H.L., FINN, R., SCHUETTE, F. Estimating recent carbon monoxide exposures. A rapid method. *Archives of Environmental Health* 5(4): 308–318, October 1962.

(*57*) RONAN, G., RUANE, P., GRAHAM, I.M., HICKEY, N., MULCAHY, R. The reliability of smoking history amongst survivors of myocardial infarction. *British Journal of Addiction* 76(4): 425–428, December 1981.

(*58*) ROSE, G. A controlled trial of the effects of health education in high-risk subjects. *Annales des Societes Belges de Medecine Tropicale* 50(4): 481–488, 1970.

(*59*) ROSE, G. Physician counseling and personal intervention. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). *Health Consequences, Education, Cessation Activities, and Governmental Action.* Volume II. Proceedings of the Third World Conference on Smoking and Health, New York City, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)77–1413, 1977, pp. 515–523.

(*60*) ROSE, G., HAMILTON, P.J.S. A randomised controlled trial of the effect on middle-aged men of advice to stop smoking. *Journal of Epidemiology and Community Health* 32(4): 275–281, December 1978.

(*61*) ROSE, G., HAMILTON, P.J.S., COLWELL, L., SHIPLEY, M.J. A randomised controlled trial of anti-smoking advice: 10-year results. *Journal of Epidemiology and Community Health* 36(2): 102–108, June 1982.

(*62*) ROSE, G., HELLER, R.F., PEDOE, H.T., CHRISTIE, D.G.S. Heart disease prevention project: A randomised controlled trial in indstry. *British Medical Journal* 1(6216): 747–751, March 15, 1980.

(*63*) SALONEN, J.T., HEINONEN, O.P., KOTTKE, T.E., PUSKA, P. Change in health behaviour in relation to estimated coronary heart disease risk during a community-based cardiovascular disease prevention programme. *International Journal of Epidemiology* 10(4): 343–354, December 1981.

(*64*) SALONEN, J.T., PUSKA, P., KOTTKE, T.E. Smoking, blood pressure and serum cholesterol as risk factors of acute myocardial infarction and death among men in eastern Finland. *European Heart Journal* 2(5): 365–373, 1981.

(65) SALONEN, J.T., PUSKA, P., KOTTKE, T.E., TUOMILEHTO, J. Changes in smoking, serum cholesterol and blood pressure levels during a community-based cardiovascular disease prevention program—the North Karelia Project. *American Journal of Epidemiology* 114(1): 81–94, July 1981.

(66) SCHACHTER, S. Recidivism and self-cure of smoking and obesity. *American Psychologist* 37(4): 436–444, April 1982.

(67) SCHWARTZ, J.L. A critical review and evaluation of smoking control methods. *Public Health Reports* 84(6): 489–506, June 1969.

(68) SCHWARTZ, J.L. *Smoke Watchers Evaluation (Preliminary Report).* Unpublished report, Institute of Health Research, Berkeley, 1973.

(69) SCHWARTZ, J.L. Research methodology in smoking cessation: A critique. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). *Health Consequences, Education, Cessation Activities, and Governmental Action.* Volume II. Proceedings of the Third World Conference on Smoking and Health, New York City, June 2–5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)77–1413, 1977, pp. 649–653.

(70) SCHWARTZ, J.L., DUBITZKY, M. *Psychosocial Factors Involved in Cigarette Smoking Cessation.* Berkeley, Institute of Health Research, Permanente Medical Group, Kaiser Foundation Health Plan, 1968.

(71) SHIPLEY, R.H., ROSEN, T.J., WILLIAMS, C. Measurement of smoking: Surveys and some recommendations. *Addictive Behaviors* 7(3): 299–302, 1982.

(72) STEWART, R.D. The effect of carbon monoxide on humans. *Annual Review of Pharmacology* 15: 409–423, 1975.

(73) STRAITS, B.C. The discontinuation of cigarette smoking: A multiple discriminant analysis. In: Zagona, S.V. (Editor). *Studies and Issues in Smoking Behavior.* University of Arizona Press, Tucson, 1967, pp. 79–81.

(74) TUOMILEHTO, J., KOSKELA, K., PUSKA, P., BJORKQVIST, S., SALONEN, J. A community anti-smoking programme: Interim evaluation of the North Karelia Project. *International Journal of Health Education* 21(4, Supplement): 3–15, October-December 1978.

(75) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79–50066, 1979, 1136 pp.

(76) WALD, N.J., IDLE, M., BOREHAM, J., BAILEY, A. Carbon monoxide in breath in relation to smoking and carboxyhaemoglobin levels. *Thorax* 36(5): 366–369, May 1981.

(77) WALLACE, N.D., DAVIS. G.L., RUTLEDGE, R.B., KAHN, A. Smoking and carboxyhemoglobin in the St. Louis metropolitan population. *Archives of Environmental Health* 29(3): 136–142, September 1974.

(78) WERKO, L. Prevention of heart attacks. A multifactorial preventive trial in Gothenburg, Sweden. *Annals of Clinical Research* 11(2): 71–79, April 1979.

(79) WILHELMSEN, L. Risk factors for disease according to population studies in Göteborg, Sweden. Paper presented at Skandia International Symposia, September 23–25, 1980. In: Bostrom, H., Ljungstedt, H. (Editors). *Medical Aspects of Mortality Statistics.* Almquist and Wiksell International, Stockholm, Sweden, 1981, pp. 73–88.

(80) WILHELMSEN, L., TIBBLIN, G., WERKO, L. A primary preventive study in Gothenburg, Sweden. *Preventive Medicine* 1(1–2):153–160, March 1972.

(*81*) WORLD HEALTH ORGANIZATION EUROPEAN COLLABORATIVE GROUP. An international controlled trial in the multifactorial prevention of coronary heart disease. *International Journal of Epidemiology* 3(3): 219–224, September 1974.

(*82*) ZEIDENBERG, P., JAFFE, J.H., KANZLER, M., LEVITT, M.D., LANGONE, J.J., Van VUNAKIS, H. Nicotine: Cotinine levels in blood during cessation of smoking. *Comprehensive Psychiatry* 18(1): 93–101, January/February 1977.

SECTION 8. THE EFFECT OF CIGARETTE SMOKING CESSATION ON CORONARY HEART DISEASE

Epidemiologic Evidence Regarding Smoking Cessation and Coronary Heart Disease

The epidemiologic data on smoking and coronary heart disease (CHD) were reviewed in detail in a preceding section, as well as in the Reports of the Surgeon General for 1964, 1971, and 1979 (*60, 61, 62*). Coronary heart disease (ICD/6 and ICD/7 No. 420) before 1968 and ischemic heart disease (ICD/8 and ICD/9 Nos. 410–414) since 1968 are considered synonymous with one another for all practical purposes and are abbreviated as CHD. Terminology and data on CHD are discussed in detail elsewhere (*33, 34, 44*). This discussion is limited to epidemiologic data on smoking cessation and CHD. Several prospective studies involving self-selected questionnaire respondents include extensive epidemiologic data on smoking cessation and CHD mortality. The results, summarized in Table 1, show CHD death rates for former smokers relative to never smokers as a function of the number of years stopped smoking cigarettes, generally determined as of the time the questionnaire was completed. Data in this form are available only for men, generally white men. The studies are as follows: the British physicians study, including 10-year followup (*10, 11*) and 20-year followup (*12*); the American Cancer Society 9-State study (*22, 23*) and the American Cancer Society 25-State cancer prevention study (*20, 21*); the U.S. veterans study with 8.5-year followup (*32*) and 16-year followup (*49*); and the Swedish representative sample study with 10-year followup (*4*). Excluded were numerous studies that present data only on former smokers as a whole or have data on a few special categories of former smokers, such as Shapiro et al. (*58*) and Hirayama and Hamano (*25*). Much of these other epidemiologic data on former smokers is summarized in the 1979 Report of the Surgeon General on Smoking and Health (*60*) and in the preceding section of this Report on coronary heart disease.

Numerous epidemiologic studies (*10, 11, 12, 14, 20, 21, 32*) have shown a decrease in CHD mortality for ex-smokers compared with continuing smokers, and it has been suggested that smoking cessation accounts for this salutary effect. Another view (*57*) has been that continuing smokers and quitters are somehow constitutionally different and that their health experiences might also be different, independent of smoking status. Two prospective studies of current smokers, some of whom became persistent quitters during the course of the study, show that persistent quitters have lower CHD and total death rates than do continuing smokers (*17, 18*). Friedman et al. (*17*) examined this question in some detail in the Kaiser-Permanente study of over 25,000 persons. They compared 18 baseline characteristics related to coronary disease in quitters and continuing smokers at a time when all were smoking. They found that the beneficial effects of quitting on CHD mortality could not be explained by differences in their baseline characteristics (Table 2).

TABLE 1.—Male coronary heart disease and total mortality ratios for current and former cigarette smokers relative to never smokers, as a function of years stopped smoking

Overall cohort description	Smoking selection criteria	Years stopped[1]	Coronary heart disease mortality ratio[2]			All causes mortality ratio[2]		
British physicians[3]	Cigarettes only	0	1.41 (464)			1.37 (1566)		
		1–4	1.05 (28)			0.96 (71)		
		5–9	1.25 (61)			1.18 (204)		
		10–14	1.16 (59)			1.12 (204)		
		15+	1.12 (40)			1.11 (153)		
		NS	1.00 (113)			1.00 (436)		
			Attained age			Attained age		
			30–54	55–64	65+	30–64	65+	30+
British physicians[4]	Cigarettes only, at least 5 years	0	3.5	1.7	1.3	2.0	1.6	1.8
		1–4	1.9 (7)	1.9 (19)	1.0 (24)	1.7 (67)	1.4 (99)	1.5 (166)
		5–9	1.3 (10)	1.4 (34)	1.3 (76)	1.6 (141)	1.4 (242)	1.5 (383)
		10–14	1.4 (10)	1.7 (38)	1.2 (62)	1.4 (104)	1.2 (206)	1.3 (310)
		15+	1.3 (7)	1.3 (45)	1.1 (148)	1.1 (106)	1.1 (484)	1.1 (590)
		NS	1.0 (32)	1.0 (75)	1.0 (182)	1.0 (326)	1.0 (611)	1.0 (937)
			Cigarettes smoked per day			Cigarettes smoked per day		
			1–19	20+		1–19	20+	
American Cancer Society 9-State study[5]	Cigarettes only	0	1.75 (604)	2.20 (604)		1.61 (2303)	2.02 (1326)	
		<1	2.10 (23)	3.00 (18)		2.04 (51)	2.69 (35)	
		1–9	1.54 (80)	2.06 (64)		1.30 (159)	1.82 (135)	
		10+	1.09 (40)	1.60 (40)		1.08 (141)	1.50 (87)	
		NS	1.00 (709)	1.00 (709)		1.00 (1644)	1.00 (1644)	

TABLE 1.—Continued.

Overall cohort description	Smoking selection criteria	Years stopped[1]	Coronary heart disease mortality ratio[2]		All causes mortality ratio[2]	
			Cigarettes smoked per day for initial ages 40–79		Cigarettes smoked per day for initial ages 50–74	
			1–19	20+	1–19	20+
American Cancer Society 25-State study[6]	Cigarettes only	0	1.90 (1063)	2.55 (2822)	1.72 (2015)	1.94 (3741)
		<1	1.62 (29)	1.61 (62)	1.61 (64)	2.18 (213)
		1–4	1.22 (57)	1.51 (154)	1.44 (144)	1.98 (499)
		5–9	1.26 (55)	1.16 (135)	1.34 (128)	1.49 (416)
		10–19	0.96 (52)	1.25 (133)	1.02 (255)	1.32 (546)
		20+	1.08 (70)	1.05 (80)		
		NS	1.00 (1841)	1.00 (1841)	1.00 (3512)	1.00 (3512)
			Attained age, 55–64		Attained age, 55–64	
U.S. veterans[7]	Cigarettes with or without cigars/pipes, stopped for other than doctor's orders	0	1.66 (3064)		1.72 (6928)	
		1–4	1.34 (155)		1.56 (379)	
		5–9	1.47 (279)		1.42 (596)	
		10–14	1.13 (161)		1.28 (365)	
		15+	0.97 (342)		1.07 (779)	
		NS	1.00 (1218)		1.00 (2617)	
			Attained age, 31–99		Attained age, 31–99	
U.S. veterans[8]	Cigarettes with or without cigars/pipes, stopped for other than doctor's orders	0	1.58 (13,845)		1.73 (36,143)	
		1–4	1.35 (150)		~1.5 (384)	
		5–9	1.38 (599)		~1.4 (1441)	
		10–14	1.29 (997)		~1.3 (2445)	
		15–19	1.21 (1101)		~1.2 (2767)	
		20+	1.05 (2418)		~1.05 (6049)	
		NS	1.00 (~6500)		1.00 (16,224)	

TABLE 1.—Continued.

Overall cohort description	Smoking selection criteria	Years stopped [1]	Coronary heart disease mortality ratio [2]			All causes mortality ratio [2]		
			Years smoked cigarettes, initial age, 40–69			Years smoked cigarettes, initial age, 40–69		
			< 20	≥ 20	Total	< 20	≥ 20	Total
Swedish representative sample [9]		0			1.7 (212)			1.4 (557)
		1–9	0.9 (7)	1.6 (84)	1.5 (97)	1.0 (26)	1.4 (212)	1.3 (253)
		10+	0.9 (40)	1.1 (46)	1.0 (86)	1.0 (123)	1.0 (117)	1.0 (241)
		NS	1.0 (219)	1.0 (219)	1.0 (219)	1.0 (671)	1.0 (671)	1.0 (671)

[1] Years stopped smoking was measured as of beginning of followup, except for the U.S. veterans study, where the number of years stopped was increased by 1 with the passage of each calendar year unless death occurred. 0 years stopped denotes current smoker; NS denotes never smoker.

[2] Mortality ratio is former smoker death rate relative to never smoker death rate, properly adjusted for age; ratio for never smokers is defined to be 1.0. Number of deaths are in parentheses.

[3] Study of 34,445 men aged 20+, at 10-year followup, 1951–1961. Doll and Hill (*10, 11*).

[4] Study of 34,440 men aged 20+, at 20-year followup, 1951–1971. Doll and Peto (*12*).

[5] Study of 187,783 men aged 50–69, at 44-month followup, 1952–1955. Hammond and Horn (*22, 23*).

[6] Study of 440,558 men aged 30+, approximately at 4-year followup, 1959–1963, for total mortality, and 358,534 disease-free men at 6-year followup, 1959–1965, for CHD mortality Hammond (*20*), Hammond and Garfinkel (*21*).

[7] Study of 248,046 men aged 31–84, at 5.5-year or 8.5-year followup, 1954–1962. Kahn (*32*).

[8] Study of 248,045 men aged 31–84, at 13-year or 16-year followup, 1954–1969. Rogot and Murray (*49*).

[9] Study of 51,911 men aged 18–69, at 10-year followup, 1963–1972. Cederlof et al. (*4*).

People who persisted in cigarette smoking had more than twice the risk of dying from CHD than those who quit even after taking into account the other baseline differences. These studies provide stronger evidence regarding the benefits of quitting than do the studies in which all of the ex-smokers had stopped smoking before the beginning of the followup.

Data from two "natural experiments" of smoking cessation among physicians in Britain (*12*) and in California (*14*) are presented in Table 3. Because these physicians have stopped smoking to a much greater extent than has the general male population, the subsequent CHD mortality trend in physicians as a whole relative to the general population constitutes a crude estimate of the overall mortality benefits of smoking cessation. This assumes that there have been no other major risk factor changes in the compared populations, but unfortunately, other risk factors were not measured in these two studies. Both studies support the earlier prospective studies with regard to the benefits of smoking cessation on CHD mortality. In addition, they show the benefit of smoking cessation among a cohort as a whole, including the continuing smokers with the quitters.

The most straightforward interpretation of ex-smoker data indicating that CHD mortality rates of persons who stopped smoking are substantially lower than those of persons who continued smoking, is that smoking cessation directly results in the reduction of risk of heart disease mortality. Underlying this presumed CHD benefit is the assumption that ex-smokers are a representative sample of smokers, except that they have stopped smoking. If the assumption of representativeness is not valid and significant baseline differences in relevant factors exist between ex-smokers and smokers, then the mortality comparison of ex-smokers and continuing smokers may not properly describe the benefits of smoking cessation for the typical smoker. In the Kaiser-Permanente study (*17*), there were small differences in risk profiles and other factors between those who continued to smoke and those who quit, but these differences were not large enough to account for the differences in CHD death rates.

In summary, each of the several major prospective studies of smoking cessation demonstrates that ex-cigarette smokers have a decreased risk of subsequent mortality relative to continuing smokers. The decreased risk occurs fairly quickly after cessation of smoking, suggesting that the effects of cigarette smoking are reversible. The quitters were self-selected in these observational studies, however, and may include cigarette smokers at lower risk of disease. However, the steadily decreasing risk over time after quitting suggests that more is going on than the simple selection of a lower risk group. Conversely, some smokers may quit in response to symptoms or diagnosis of smoking-related illness, thus possibly

TABLE 2.—Age-, sex-, and race-adjusted death rates according to smoking category and selected major causes

Category	No. of subjects	No. of person-years	Adjusted death rate per thousand person-years[1]					
			All causes	All causes except injuries and poisoning	All neoplasms	Lung cancer	All circulatory diseases	Coronary heart disease
Persistent smokers	9,394	70,348	9.2 (557)	8.1 (485)	3.2 (191)	0.9 (58)	4.0 (240)	2.6 (168)
Temporary quitters	970	6,666	7.1 (46)	6.7 (43)	2.2 (14)	0.9 (6)	3.8 (24)	2.3 (16)
Persistent quitters	2,856	18,798	5.3 (107)	5.0 (102)	1.9 (39)	0.3 (6)	2.2 (46)	1.4 (31)
Never smokers	12,697	99,290	5.1 (569)	4.8 (540)	1.8 (199)	0.02 (2)	2.4 (275)	1.6 (186)

[1] Figures in parentheses denote number of deaths.

Source: Friedmen et al. (*17*).

TABLE 3.—Relative trends in cigarette smoking and coronary heart disease mortality among male physicians in Britain and California in two natural experiments of smoking cessation, where status of other risk factors is unknown

British male physicians, 1951–71[1]

	Time period			
	1951–55	1956–60	1961–65	1966–71
Percentage of physician current smokers at start of time period	41	33	27	21
Ratio of smokers (physicians/British males)	88	68	60	51
	Standardized mortality ratio (physicians/British males)			
CHD and myocard. degen., attained age				
20–54		107	85	62
55–64		120	103	86
65–74		109	100	91
75–84		88	94	100
All causes, attained age				
20–64		82	76	70
65–84		75	77	78

California male physicians, 1950–79[2]

	Time period					
	1950–54	1955–59	1960–64	1965–69	1970–74	1975–79
Percentage of physician current smokers at start of time period	53	48	39	28	20	14
Ratio of smokers (physicians/U.S. males)	100	83	66	55	44	35
	Standardized mortality ratio (physicians/U.S. males)					
CHD	115	97	86	80	74	69
All causes	89	80	79	78	67	67

[1] Study of 34,440 men aged 20+, followed for 20 years. Doll and Peto (*12*).
[2] Study of 10,310 men aged 25+, followed for 30 years. Enstrom (*14*).

underestimating the benefits of quitting that would be expected in an otherwise healthy population. Other variables that may contribute to mortality may not have been included in the analysis.

Randomized Controlled Trials of CHD Prevention Not Involving Smoking Cessation

The most rigorous way to determine the value of smoking cessation is the randomized controlled trial. A series of important experimental or clinical trials have been conducted in the United States and other countries over the past 25 years in order to

establish the effectiveness of primary prevention of CHD through modification of risk factors. These randomized controlled trials involve both primary and secondary prevention (*2*). The primary prevention trials select subjects who are free of CHD or stroke at entry to the study. The secondary prevention trials attempt to modify risk factors after a heart attack or stroke in order to reduce the risk of a second heart attack or death (*6, 7, 8, 38, 40*). Secondary prevention trials and nonrandomized trials are not discussed further here.

Most previous primary prevention trials of CHD have been limited to a single risk factor such as serum cholesterol reduction. Many single risk factor intervention trials include a pharmacologic agent that lowers either serum cholesterol or blood pressure and is compared with a placebo. Most of these studies are further limited to higher risk subjects, such as subjects with serum cholesterol levels in the highest 10 to 15 percent of the population, or to relatively small sample sizes. They did not monitor or control for changes in cigarette smoking habits.

The most extensive primary prevention trials involve dietary reduction of cholesterol; they are described in more detail elsewhere (*2, 39*). The major randomized trials are the Los Angeles veterans domiciliary study (*9*), the Helsinki, Finland, mental hospital study (*42, 59*), and a feasibility study of free-living and institutionalized Americans (*45*). Each of these studies involved about 200 to 400 men in the dietary intervention group and a similar number in the control group.

Another set of randomized trials has involved reduction of high blood pressure using antihypertensive medication—the U.S. Veterans Administration cooperative study (*63*), the U.S. hypertension detection and followup program (*30, 31*), the Australian therapeutic trial (*1*), and the Oslo drug trial (*24*). These large studies followed three small studies—Hamilton et al. (*19*), Wolff and Lindeman (*67*), and the Cooperative Randomized Control Trial (CRCT) (*5*). These studies generally show that lowered blood pressure results in some reduction in CHD among the treated groups relative to the control groups.

Intervention Trials of CHD Prevention Involving Smoking Cessation

The observational epidemiological studies strongly suggest that cigarette smoking cessation decreases the risk of heart attack and CHD mortality compared with the risk for continuing smokers (*60, 61, 62*). All of the observational studies, however, have the limitation that the individuals were not experimentally assigned to smoking and nonsmoking status. Experimental studies such as randomized

controlled trials offer a solution to this problem, because they test a smoking cessation intervention in the most rigorous way possible using human subjects (*2, 37, 70*). However, even in such trials, those assigned to the no-intervention group modify their smoking habits, and those assigned to the intervention group have incomplete success in quitting.

Ideally, each risk factor should be treated independently, but modification of one risk factor often results in changes in other risk factors. For instance, some studies have noted that cigarette smoking cessation can lead to a modest weight gain (*3, 26, 47*). In a good primary prevention program there would be an effort to reduce or to eliminate the weight gain that sometimes accompanies cessation. Although the multifactorial approach is less precise, it has been considered to be a more practical approach to the problem. There has been only one trial of smoking cessation per se (*50, 51*).

Two types of primary prevention trials involving smoking cessation are underway. The first type of study, exemplified by the Multiple Risk Factor Intervention Trial (MRFIT), selected subjects at high risk of CHD based on a combination of cigarette smoking history, elevated blood pressure, and high serum cholesterol level (*43*). Subjects were then randomized into either a special treatment group or a comparison group. The Whitehall study (*50, 51*) and the Oslo study (*27*) are also of this type.

In the second type of study, communities or groups rather than individuals are randomized into a treatment or a control group. The WHO heart disease study randomized men according to the factory where they work and followed the individual factory workers (*70*). The North Karelia study randomized two separate communities in Finland (*48*). Whereas the factory workers were individually followed, the communities were monitored only in a cross-sectional manner and individuals were not followed longitudinally.

The primary hypothesis in these studies is that reduction of the risk factors will reduce the incidence of and mortality from CHD. The first step in testing this hypothesis requires that the subjects or groups be successfully recruited and categorized at entry to the study and that a very high percentage be successfully followed for the duration of the study.

The second step in testing the hypothesis requires the successful reduction of the major risk factors—smoking, high blood pressure, and high serum cholesterol. Often a selected subsample of high risk subjects receives more intensive individual intervention, but the rest of the treatment group receives only community health education. It is not known how large a reduction in risk factors is necessary to observe a decrease in CHD, except that the larger the reduction in risk factor the greater the chance for a decrease in CHD. Specific goals for reduction of risk factors can be based on the presumption

that such reduction would result in a statistically significant decrease in the incidence of and mortality from CHD according to the observational epidemiologic studies. The relationship between the reduction of this risk score and actual reduction in the frequency of disease is, of course, the hypothesis being tested.

The third and most critical step depends on the first two: that is, the measurement of outcome—changes in the incidence of or death from CHD. The ability to measure the incidence requires careful and unbiased monitoring of the sample. The determination of total and cardiovascular mortality is much simpler, since it depends only on minimizing the number of participants lost to followup. The community studies attempt to compare the death rates between two or more communities, and the power of such a statistical test is obviously very weak.

Both the community studies and the individualized studies are also confounded by the uncertainty of the interval between risk factor change and reduction in risk of disease. Those subjects most likely to die or to have a heart attack in the first few years of the study are those with the most extensive disease at baseline. Unless the population is followed long enough to include both the lag period and the effects of the initial selection of those with advanced subclinical disease, a spurious interpretation of the study results is possible.

Generally, studies of experimental communitywide interventions are unlikely to determine the efficacy of smoking cessation on reducing the incidence of and mortality from CHD because of the difficulty in determining the effects of smoking cessation on specific individuals in the community and in separating out the effect of smoking cessation from other changes in the community. In many of these studies the percentage of men who reported quitting smoking is relatively small, which reduces the power of the study at least in terms of smoking cessation.

This review focuses on all intervention studies involving smoking cessation for which CHD mortality outcome data have been published. In another section of this Report a detailed review on smoking cessation in clinical and community trials is presented. Discussed in detail here are data from the U.S. Multiple Risk Factor Intervention Trial (*43*), the Whitehall study in London, England (*51*), the Oslo study in Norway (*27*), the WHO European Collaborative study (*69*), and the North Karelia project in Finland (*48*). Omitted from this section are smoking intervention studies without published mortality outcome data, such as the Stanford, California, three-community study (*16*), the Stanford five-community study (*15*), the Göteborg, Sweden, study (*64, 65, 66*), and the Helsinki, Finland, study (*46*).

Essential details from each trial are described in the following pages and tables. The initial population characteristics and risk factor changes are summarized in Table 4. The mortality outcomes in the intervention and control groups are summarized in Table 5 for coronary heart disease and total mortality. Available results are also given for other circulatory diseases, lung cancer, and other cancer. The results for the four trials involving cohort mortality followup are combined in Table 6. Coronary heart disease incidence rates from the Oslo and WHO studies are presented in Table 7. A comparison of death rates in the MRFIT intervention and control groups as a function of initial smoking status and status at 1-year followup is summarized in Table 8. Observed deaths in the MRFIT and Whitehall studies are compared with expected deaths based on general population rates in Table 9. Comparisons of reductions in CHD and total mortality from the observational studies and from the MRFIT and Whitehall studies are made in Table 10.

Randomized Controlled Trials of Individuals

Multiple Risk Factor Intervention Trial

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized controlled trial to investigate the effect of reducing cardiovascular risk factors in a group of asymptomatic men at high risk of cardiovascular disease (*43*). Out of 361,662 men initially screened, 12,866 men aged 35 to 57 were selected for the trial because they were at increased risk of death from CHD, but without clinical evidence of CHD, and agreed to be randomized and reexamined. A series of three complex screening procedures were used to select the final 12,866 men, who constituted only 3.6 percent of those screened. Men were designated as at increased risk because their levels of three risk factors—cigarette smoking, serum cholesterol, and blood pressure (BP)—were sufficiently high at a screening visit. All of these men were in the upper 15 percent of a risk score distribution based on data from the Framingham heart study; about two-thirds were in the upper 10 percent of risk. For example, a man whose diastolic BP was 90 mm Hg and who reported smoking 30 cigarettes per day was risk eligible at the 10 percent level if his serum cholesterol level was at least 295 mg/dl. The study was restricted to men, since including women, with their substantially lower risk of CHD, would have necessitated a larger study population.

The men were randomized into two groups of equal size and identical baseline characteristics from December 1973 through February 1976. A special intervention (SI) group of 6,428 men received an intensive counseling program, aimed at cessation of cigarette smoking, weight loss, and a change of diet for a reduction of elevated serum cholesterol and BP levels. A usual care (UC) group of

TABLE 4.—Basic description of smoking cessation intervention studies of males, including demographic characteristics and risk factor changes

Variable	Individual intervention			Factory intervention	Community intervention	
	MRFIT	Whitehall	Oslo	WHO	North Karelia	
					1972	1977
Number in intervention (I) group	6428	714	604	24,615	1834	1785
Number in control (C) group	6438	731	628	25,169	2665	2616
Mean age (yrs)	46.2	52.9	45.2	48.5	~42	~47
Age range (yrs)	35–57	40–59	40–49	40–49	25–59	30–64
Race (% white)	90	~100	~100	~100	~100	
Followup period: Start date	12/1973	1968–70	1972–73	1971–76	1972	
End date	2/1982	1979	1978	1982	1977	
Average length (yrs)	7	10	5	6	5	
Risk factor (RF) at start						
Cigarette smokers (%)	59	100	79.4	60	51.5	
Relative change[1]/end	-29%	-24%	-12%	-3.4%[2]	-2.5%	
Relative change/whole period	-31%	-54%	-16%	-1.9%	-[3]	
Average no./day cigarettes	20	19.3	12.7	11.2	9.4	
Relative change/end	-30%[2]	-33%	-37%	-10.1%	-9.8%	
Relative change/whole period	-30%[2]	-53%	-45%	-8.9%	–	
Serum cholesterol (mg/dl)	254	213[4]	329	217	263	
Relative change/end	-2%	–	-12%	-0.5%	-4.1%	
Relative change/whole period	-2%	–	-13%	-1.2%	–	
Blood pressure[5] (mm Hg)	91	–[4]	–[4]	138	91.5	
Relative change/end	-4%	–	–	-2.0%	-2.8%	
Relative change/whole period	-4%	–	–	-2.0%	–	
Combined change in CHD risk	-22.2%	–	–	-11.1%	-17.4%	

[1] Relative change = $(RF_I - RF_C)/RF_C$, except for North Karelia, where relative difference is determined from (I–C) 1977 and (I–C) 1972.
[2] Estimated from available data.
[3] Not measured or not reported.
[4] Risk factor is not part of intervention.
[5] Diastolic, except for systolic in WHO study.

6,438 men received annual checkups including medical history, physical examination, and laboratory studies at the MRFIT clinics, but were referred to their personal physicians or other community medical facilities for such treatment of their risk factors as was considered individually appropriate. Thus, no intervention program was offered to them. The results of their screening and annual examinations were provided to their respective physicians who were also informed as to the scientific objectives of the study.

The smoking intervention urged those SI participants who smoked cigarettes to quit, but no effort was made to alter the smoking habits of those who smoked only pipes and cigars (*29*). Dosage reduction—

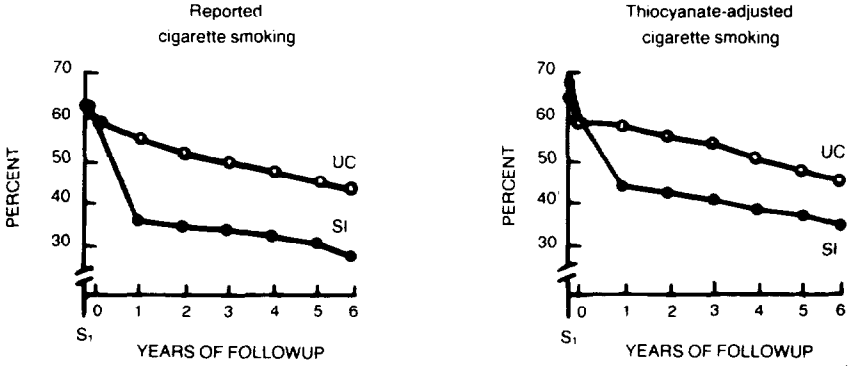


FIGURE 1.—Mean risk factor levels for cigarette smoking by year of followup for Multiple Risk Factor Intervention Trial Research Group participants

NOTE: SI indicates special intervention
UC indicates usual care
S_1 indicates first screening visit
SOURCE: Multiple Risk Factor Intervention Trial Research Group (*43*).

switching to cigarettes low in tar and nicotine—was recommended only as an intermediate step to cessation. Conventional behavior modification techniques were used throughout the trial; aversive techniques and hypnosis were used in selected instances. Ten-week group sessions at the beginning of the trial and 5-day quit clinics during the final years were found to be particularly successful intervention approaches. Further details on the smoking intervention are provided in an earlier section of this Report, and the serum cholesterol and BP interventions are described elsewhere (*43*).

Statistically significant CHD risk factor reductions between the SI and UC groups were obtained at each annual visit. Of particular interest was the reduction in number of cigarette smokers, as shown in Figure 1. At the beginning of followup, 59 percent of all men had reported themselves as current cigarette smokers. At the 12-month followup, the stated quit rates were 43 percent for SI men and 14 percent for UC men; at 72 months, the rates were 50 percent and 29 percent, respectively. Serum thiocyanate-adjusted quit rates at 12 months were 31 percent for SI men and 12 percent for UC men; at 72 months they were 46 percent and 29 percent, respectively. This means that the SI group reduced its level of smokers 30 percent more than the UC group. The risk factor changes are summarized in Table 4.

As of February 28, 1982, after an average period of followup of 7 years, there were 260 deaths among the UC men, of which 124 were ascribed to CHD and 21 to other cardiovascular causes, as summa-

rized in Table 5. There were 265 deaths among the SI men, of which 115 were ascribed to CHD and 23 to other cardiovascular causes. The key mortality endpoint of CHD was 7.1 percent less in the SI group than in the UC group, while the death rate for all causes was 2.1 percent higher for the SI men. The approximate 90 percent confidence interval (CI) for the percentage change in CHD mortality attributable to MRFIT intervention ranges from a 25 percent decrease to a 15 percent increase. There were 34 lung cancer deaths in the SI group and 28 in the UC group and 47 other cancer deaths in the SI group and 41 in the UC group.

The number of deaths in the UC group was substantially short of expectation for the 6 complete years of followup as well as for the average followup period of 7 years, as shown in Table 9. These mortality patterns appear to be similar to those seen in healthy persons selected for life insurance policies (*22, 41*). On the basis of the design risk factor change assumptions and the Framingham risk functions, 442 deaths (including 187 from CHD) were expected among the 6,438 UC men by the end of 6 years of followup, but only 219 (including 104 from CHD) occurred (50 percent of expected); about 515 deaths (including 220 from CHD) were expected after 7 years, but only 260 deaths (including 124 from CHD) occurred.

At least three possible explanations for these results must be considered: (1) such an intervention program is without benefit in terms of substantial decreases in mortality; (2) the intervention program does affect CHD mortality, but the benefit was not observed in this study, an effect of chance; or (3) one or more constituents in the intervention program may have had an unfavorable effect on survival in some subgroups, offsetting the beneficial effects of others.

Of these possible interpretations, a combination of favorable and unfavorable effects of the intervention program seems most plausible to the MRFIT investigators. Even with the unexpected sizable risk factor reduction among the UC men, the lower-than-expected UC mortality, and the duration of intervention averaging only 7 years, the likelihood that these factors resulted in missing an overall positive effect is relatively low. The data suggest that except for some groups of hypertensive persons, particularly those with resting ECG abnormalities, the MRFIT intervention is apparently associated with a lower CHD mortality in the SI group.

The MRFIT data also warrant analysis as an observational study (Table 8). Of those who had been cigarette smokers at entry, 1,365 reported quitting at year 1 interview (and had confirmatory blood SCN levels) and 6,298 did not quit. Over an average 6 years of further followup, those who quit smoking at year 1 had a 1.10 percent CHD mortality rate, while those who continued smoking had a CHD mortality rate of 2.03 percent. This corresponds to a relative risk of 0.54 (1.10/2.03) or a 46 percent lower risk of CHD death for

TABLE 5.—Comparison of deaths (d) and death rates (r) in the intervention and control groups of four randomized controlled trials

Cause of death	Intervention group		Control group		Percentage difference[2]
	r_I[1]	d_I[1]	r_C[1]	d_C[1]	$(r_I-r_C)/r_C$
MRFIT: 7-year deaths					
Coronary heart disease	.0179	115	.0193	124	-7.1
Other circulatory disease	.0036	23	.0033	21	+9.8
Lung cancer	.0053	34	.0043	28	+21.6
Other cancer	.0073	47	.0064	41	+14.8
All other causes	.0072	46	.0071	46	+0.1
All causes	.0412	265	.0404	260	+2.1
Whitehall: 10-year deaths					
Coronary heart disease	.0686	49	.0848	62	-19.1
Other circulatory disease	.0182	13	.0164	12	+11.0
Lung cancer	.0252	18	.0328	24	-23.2
Other cancer	.0392	28	.0164	12	+139.0 (p=.01)
All other causes	.0210	15	.0246	18	-14.6
All causes	.1723	123	.1751	128	-1.6
Oslo: 5-year deaths					
Coronary heart disease (Fatal MI and sudden coronary death)	.0099	6	.0222	14	-55.4
Other circulatory disease	.0033	2	.0016	1	+106.3
All cancer	.0063	5	.0127	8	-34.6
All other causes	.0050	3	.0016	1	+212.5
All causes	.0265	16	.0382	24	-30.6
WHO: 6-year deaths					
Coronary heart disease	.0150	367	.0162	355	-7.4
All other causes	.0254	630	.0253	569	+0.4
All causes	.0404	997	.0415	924	-2.7

[1] Death rate (r) equals deaths (d) divided by initial number in group.

[2] Unless indicated with a p value, differences are not statistically significant ($p > 0.05$), based on a two-tailed test for a Poisson variable.

those who quit smoking compared with those who continued. For all-cause mortality, the relative risk was 0.73 or a 27 percent lower risk for those who quit compared with those who continued to smoke.

As demonstrated in subsequent portions of Table 8, when these subjects are analyzed according to level of smoking at entry or by status in the SI or the UC group, those who quit smoking always enjoyed a substantially more favorable survival rate than those who didn't quit.

Thus, MRFIT data are entirely consistent with the numerous previous studies showing that those who quit cigarette smoking enjoy a substantially improved survival.

In conclusion, the MRFIT study has shown that it is possible to apply an intensive long-term intervention program against three

coronary risk factors with considerable success in risk factor changes. These results are accompanied by an apparent heterogeneity of effects among sizable subgroups, and there must be caution in reaching conclusions from such subgroup data. It may be relevant that multifactor intervention received a less than optimal test, owing in part to unexpected declines in risk factor levels and in part to lower-than-expected mortality in the UC group. In regard to the former, the UC men thus constituted to a considerable extent a "treated" group.

Whitehall Civil Servants Study

A randomized controlled trial was set up to provide an unbiased estimate of the consequences of smoking cessation in middle-aged men (*50, 51*). A total of 1,445 male cigarette smokers with an especially high cardiorespiratory risk were selected from 16,016 men aged 40 to 59 who had undergone a cardiorespiratory screening examination in the Whitehall study of male civil servants in London. Using a modification of the multivariate linear discriminant function coefficients that were calculated for predicting coronary heart disease (CHD) among the Framingham men aged 30 to 62, a risk score was similarly calculated for each man who smoked five or more cigarettes a day. This score ranked the smokers according to their estimated risk of major illness or death from cardiorespiratory disease. The distribution of the score was tested early in the study, and a cutoff point was determined such that the scores of 10 percent of all men and 32 percent of smokers were eligible and exceeded this value, which was thereafter used to define eligibility for the trial.

Men receiving medical care for heart disease or elevated blood pressure, those found to have either severe hypertension or diabetes mellitus, and those with major concomitant disease were excluded from the trial. Additionally, all men taking psychotropic drugs or with a record of previous psychiatric inpatient treatment were eliminated. If during the 1-year interval between initial screening and trial interview they had died, moved away, or stopped smoking, they were then not eligible for the study. The remaining 1,445 high risk eligible cigarette smokers were randomly allocated to study groups; 714 men composed the intervention group, and 731 men were in the normal care group.

Men in the intervention group were recalled for a series of personal interviews with the physician. First, each received a letter inviting him to an appointment to discuss the results of his previous examination. At that visit the reason for recall was presented: evidence in his particular case that smoking represented more than the average risk to his future health, not the discovery of disease. The scientific evidence that stopping smoking was likely to bring benefits was explained and illustrated by charts, with the emphasis

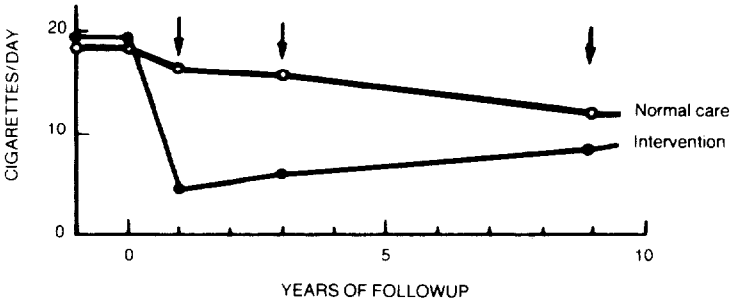


FIGURE 2.—Mean daily cigarette consumption by year of followup for the Whitehall intervention study

SOURCE: Rose et al. (*51*).

throughout on the evidence for the positive benefits and practicalities of stopping rather than on the hazards of continuing to smoke.

A full report of the screening examination results and information that further action was in his hands was sent to the practitioners of men in the normal care groups. The men were not made aware that they were involved in a trial. At the 1-year and 3-year points in the study, they were asked to return for an examination to help research. Examinations were popular because most men saw them as beneficial checkups. The questionnaire response rates among survivors were 84 percent at 1 year and 83 percent at 9 years. Dropouts were mainly retirees. The proportion of responders in the intervention group who were not smoking any cigarettes was 63 percent at 1 year, decreasing to 55 percent at 9 years; initially, all of those in the study were smokers. Figure 2 shows the trends in stated numbers of cigarettes smoked in the intervention group. After 1 year, consumption in the intervention group was one-quarter of the normal care group level. By 9 years, the estimate of cigarette consumption for intervention men was 70 percent of that for the normal care controls. Over the 10 years, the net apparent reduction in the intervention group averaged 7.6 cigarettes/day (–53 percent), compared with the control level, as shown in Figure 2 and Table 4.

During the 10 years of followup, there were 128 deaths in the control group compared with about 130 deaths expected from the age-specific rates for England and Wales in 1974, as shown in Table 9. The fact that all men entering the trial were high risk smokers should have increased the observed deaths, but this may have been offset by the "healthy worker" effect in an occupational study group or by the selection process that excluded very sick men. Deaths were also close to national levels for coronary heart disease (111 observed, 94 expected), lung cancer (42 observed, 35 expected), and other

TABLE 6.—Summary of deaths and intervention/control differences from coronary heart disease, all other causes, and all causes in four randomized controlled trials

Disease	Observed deaths in intervention group	Expected deaths based on control group	Percentage difference[1] (O–E)/E
Coronary heart disease			
MRFIT	115	123.8	-7.1
Whitehall	49	60.6	-19.1
Oslo	6	13.3	-55.4
WHO	367	396.4	-7.4
Unweighted total	537	594.1	-9.6 (p=.02)
All other causes			
MRFIT	150	135.8	+10.5
Whitehall	74	64.4	+14.9
Oslo	10	9.7	+3.1
WHO	630	627.7	+0.4
Unweighted total	864	837.6	+3.2
All causes			
MRFIT	265	259.6	+2.1
Whitehall	123	125.0	-1.6
Oslo	16	23.0	-30.6
WHO	997	1024.1	-2.7
Unweighted total	1401	1431.7	-2.1

[1] Unless indicated with a p value, differences are not statistically significant ($p > 0.05$), based on a two-tailed test for a Poisson variable.

cancers (40 observed, 41 expected). Seventy-two percent of deaths occurred in a hospital, and in 45 percent there was an autopsy. Additional data were obtained from the National Cancer Register of cases histologically confirmed either by biopsy or at autopsy for deaths from other causes.

Table 5 shows that the 10-year CHD death rate was 8.5 percent (62 deaths) for the normal care group and 6.9 percent (49 deaths) for the intervention group, a proportionate change of −19 percent (95 percent confidence limit of −43 to +18 percent). Among the 369 men who entered the trial with evidence of myocardial ischemia (angina pectoris, history of possible myocardial infarction, or positive electrocardiogram) the reduction was −23 percent compared with −11 percent in those without such evidence. The number of deaths from cardiovascular causes other than CHD was 12 in the normal care group and 13 in the intervention group.

Mortality from all causes was initially higher (though not significantly so) in the intervention group, but during the last 6 years of the trial, the rates were higher in the normal care group. During the whole 10 years, 123 intervention men (17.2 percent) died, compared

with 128 (17.5 percent) of the normal care group—a proportionate change of –2 percent (95 percent confidence limits of –22 percent to +23 percent). Causes of death were also grouped according to whether or not they were smoking related. The smoking-related causes included coronary heart disease, chronic bronchitis, and cancers of the respiratory tract, esophagus, urinary tract, and pancreas. There were 92 such deaths in the normal care group and 81 in the intervention group, a proportionate change of –9 percent (95 percent confidence levels of –31 percent to +20 percent).

The trial was designed to test whether the total reduction in cardiorespiratory disease among middle-aged men was as large as that indicated by the observational studies of ex-smokers. Its size was planned in the expectation that incidence as well as mortality data would be available; when this proved unattainable, the resultant loss of power was partly offset by extending the mortality followup to 10 years.

At 1-year followup, almost two-thirds of the intervention subjects had given up cigarettes altogether, while others claimed to be smoking less than before. Unlike the MRFIT study, objective tests of smoking behavior were not made here. However, the authors felt that those who reported complete cessation were generally truthful, while those claiming to have cut down may have been exaggerating. The reports were based on questionnaires completed at home, with little external pressure; they were largely consistent over the ensuing years. The progressively narrowing gap between the two groups was due mainly to a gradual reduction in smoking by the normal care men. Although the size of the gap may have been overestimated, there is no doubt that throughout the earlier years of the trial it was large.

Over the trial as a whole, the intervention group's level of total smoking exposure was estimated as about half that of the normal care group, implying that the effects of complete cessation might be substantially more than those observed in the trial. The results for total mortality represented the approximate balance of a favorable trend for smoking-related diseases and an adverse trend for non-lung cancers. After an exhaustive analysis of the data, the Whitehall investigators think the difference in non-lung-cancer mortality in this trial was more likely due to chance than to an effect of intervention. Such evidence as there is for the latter view should be considered as a hypothesis for further study, not as the basis for conclusions or for any recommendation to smokers.

Oslo Study

The purpose of the Oslo study was to find out whether the cessation of smoking and the lowering of high levels of blood lipids by dietary changes, if maintained for many years, would lead to

reduction in the incidence of first attacks of CHD in men aged 40 to 49 (*26, 27, 28*). All Oslo men aged 40 to 49 were invited for screening of coronary risk factors during 1972–73, and 65 percent (16,202 men) attended. From this cohort, healthy normotensive men were selected for a controlled trial if they had serum cholesterol levels (mean of two measurements) of 290 to 380 mg/dl, coronary risk scores (based on cholesterol levels, smoking habits, and blood pressure) in the upper quartile of the distribution, and systolic blood pressures (mean of two measurements) below 150 mm Hg. Those selected had normal ECGs at rest and were free of any cardiovascular disease, chest pain on exercise, clinical diabetes mellitus, fasting blood sugar levels above 135 mg/dl, cancer, disabling disease, psychopathological disease, and alcoholism.

Men who met the selection criteria were sent a letter explaining the experimental design of the trial; 97 percent were found willing to participate. There were no significant differences between the intervention and control groups for subject factors such as age, history of CHD symptoms, cigarette consumption and smoking status, serum cholesterol and triglyceride, systolic blood pressure, and diet. After the screening examination, two reexaminations were made before randomization, the first of these when the subjects were fasting.

Each of the men in the intervention group was individually talked with for 10 to 15 minutes by the investigator and introduced to the risk factor concept and the purpose of the study. Anti-smoking advice was given individually to all smokers in the intervention group. They were informed that cessation of smoking might be of special importance for those with high blood lipid levels. In addition, the dietitian established a diet record for each man and gave extensive dietary advice based on this record. Other risk factors were not subjected to intervention. Followup exams were made every 6 months for intervention subjects and every 12 months for controls.

The intervention of advice on smoking and eating habits resulted in changes in risk variables. Tobacco consumption, expressed as the number of cigarettes smoked per man per day, fell about 45 percent more in the intervention group than in the controls, as seen in Table 4. Pipe smoking was included, taking one pack of pipe tobacco weekly to equal seven cigarettes daily. The percentage of cigarette smokers fell by only 16 percent more. The data were assessed by a questionnaire and by the thiocyanate method. The mean difference in serum cholesterol between the two groups during the 5 years was 13 percent.

As the design of the study was based on CHD evidence, events of myocardial infarction (MI) plus sudden death were most important. CHD mortality (fatal MI plus sudden coronary deaths) was 55 percent lower in the intervention group as compared with the

TABLE 7.—Comparison of coronary heart disease incidence rates (r) and cases (n) in two randomized controlled trials

	Intervention group		Control group		Percentage difference[1]
	r_I	n_I	r_C	n_C	
Oslo: 5-year results					
Fatal MI and sudden coronary deaths	.0099	6	.0222	14	-55.4
Nonfatal MI	.0215	13	.0350	22	-38.6
Total CHD incidence	.0314	19	.0573	36	-45.2 (p=.03)
WHO: 6-year results					
Fatal MI and sudden coronary deaths	.0150	367	.0162	355	-7.4
Nonfatal MI	.0195	406	.0203	401	-3.9
Total CHD incidence	.0318	773	.0331	756	-3.9

[1] Unless indicated with a p value, differences are not statistically significant ($p > 0.05$), based on a two-tailed test for a Poisson variable.

control group, but the difference was not statistically significant ($p > 0.05$), as shown in Tables 5 and 7. Total CHD incidence, which included fatal and nonfatal MI and sudden death, was 45 percent lower in the intervention group than in the control group, and this difference was significant ($p < 0.05$), as shown in Table 7. This is the only trial to date to show a significant reduction in CHD incidence. All cases of sudden death satisfied the diagnostic criteria for coronary death except one unexplained sudden death. The total coronary deaths, which included fatal MI and sudden death, were lower, but not significantly lower in the intervention group than in the control group.

An estimate was made of the proportion of the difference in total CHD incidence between the two groups (36 versus 19 cases) due to the reduction in cigarette consumption and of the proportion due to the reduction in serum cholesterol using logistical regression techniques (*28*). The percentage of the decline in incidence that was due to reduction in cigarette consumption was estimated to be 26 percent among smokers only, predicting a difference between groups of 3.9 cases, out of a total difference of 17 CHD cases. Similar procedures indicated that the percentage due to cholesterol changes was 60 percent for all men, predicting a difference in CHD incidence of 10.1 cases. It seems, therefore, that the change in cigarette consumption caused about 25 percent of the difference in CHD incidence between the two groups and that the difference was due mainly to the reduction in serum cholesterol. The difference between the groups was 17 cases: 14 can be explained by this analysis, and the other 3 cases may be due to unexplained intervention effects or to chance.

Community-Based Intervention Trials

WHO European Collaborative Trial

As set out in the recent WHO report on the prevention of coronary heart disease (*70*), effective prevention must involve the population as a whole: A high incidence in the population reflects a mass elevation of risk factors, and most cases of the disease occur in the large number of people with moderate elevations rather than in the high risk minority. The first issue of public health policy, therefore, is to know the effect of population-based prevention, using resources that could reasonably be afforded. Thus, a trial of CHD prevention has been undertaken by collaborators in Belgium, Italy, Poland, Spain, and the United Kingdom (*68, 69*). It involved the random allocation of 44 factory pairs, employing 63,732 men aged 40 to 59, either to a cardiovascular screening and health education intervention program or to a control group. Separate analyses have been prepared for Belgium factories (*35, 36*) and United Kingdom factories (*52, 53*), but these subgroups are not discussed in detail here.

Randomization of individuals in a trial of community health education is not feasible, so a somewhat unusual design was used that randomized entire communities, which in this trial were factories or other large industrial groups. They were arranged in matched pairs and randomized, one to intervention and the other to serve as a control. All men aged 40 to 59 in the intervention factories were invited to complete a questionnaire and take part in a simple cardiovascular screening examination during working hours; 87 percent responded. On the basis of a multifactorial scoring system for risk factor levels (age, job activity, cigarettes smoked per day, systolic blood pressure, and serum cholesterol), 15 percent or more of the men in each factory were designated as high risk. A general campaign of risk factor modification was undertaken with posters, brochures, personal letters, progress charts, and group discussions and included advice on reducing or stopping cigarette smoking, losing weight, lowering serum cholesterol, and increasing leisure physical activity. The high risk men received more individual attention, in addition to the general educational program, including a series of personal sessions with the factory or project physician. All men with mild hypertension were treated with diuretics or other drugs in the factory or were referred to a personal physician. Drugs were not employed to lower serum cholesterol. Annually, a random sample of men was rescreened. All high risk men were seen at every anniversary in some centers, or in other centers, at particular anniversaries. All men remaining in employment at the end of the 5- or 6-year intervention period were offered a final examination.

In the control factories, a 10 percent random sample of men was screened initially, and the same 10 percent were asked to return after 2 years, again at 4 years, and then at the final screening at 5 or

6 years, when all remaining men in the original cohort, aged 40 to 59 at the start, were offered screening. It was therefore possible to compare risk factor levels at the start between all screened intervention men and 10 percent of controls, between a 5 percent random sample or more of the intervention men and the same 10 percent of the controls at 2 years and 4 years, and between all remaining men in both sets of factories at the final screening. Numbers were reduced by death, by leaving employment, and by nonresponse to the invitation on the screening day. The risk factor score used in each intervention factory to designate high risk men was applied to the 10 percent of the screened men in the paired control factory in order to identify those who would act as high risk controls for purposes of measuring risk factor change. Incidence and mortality results are now available (*69*) from this controlled trial, involving randomization of 66 factories (49,781 men) in the United Kingdom, Belgium, Italy, and Poland (Cracow). Results for Poland (Warsaw) are not yet complete, and the results have been separately presented for the United Kingdom (*53*) and Belgium (*35*). Net average reductions in risk factors (all subjects) were 8.9 percent for daily cigarettes, 1.2 percent for serum cholesterol, 0.4 percent for weight, 2.0 percent for systolic blood pressure, and 11.1 percent for a combined CHD risk estimate. Greater reductions occurred in high risk subjects (19.4 percent for the combined CHD risk estimate).

Tables 5 and 7 show that the net overall changes in CHD rates were –7.4 percent (95 percent confidence interval from –29 to +15 percent) for deaths (722 deaths) and –3.9 percent (95 percent confidence interval from –10 to +2 percent) for fatal CHD plus nonfatal myocardial infarction (1,502 cases). Among men aged 40 to 49 the reduction for this end-point was 15 percent; at ages 50 to 59 there was a small net increase. Deaths from all causes after an early adverse trend showed a –2.7 percent change overall. There were large differences between centers, ranging from a 5 percent net increase in CHD for the United Kingdom to a decrease of 24 percent in Belgium. In Belgium the decrease both in CHD incidence and in all deaths was significant at the 5 percent level (*35*). The effect on CHD in the different centers correlated broadly with their changes in risk factors. The authors concluded that a reduction in major coronary risk factors in industrial populations is possible, but it depends on adequate resources. The results support the hypotheses that CHD risk in middle-aged men is reversible and that community intervention can be beneficial; however, additional followup is necessary to determine if there are statistically significant reductions in CHD and total mortality commensurate with the risk factor changes in the entire factory population.

North Karelia Study

The purpose of the North Karelia, Finland, project was to provide a systematic comprehensive community program to reduce the currently high mortality and morbidity from CHD, primarily by reducing the known cardiovascular risk factors of smoking, serum cholesterol, and blood pressure, while promoting early detection, treatment, and rehabilitation in people with severe CHD (*48, 54, 56*). The focus was on middle-aged males; women were included, but are not discussed here. A further test was made of the feasibility and the effect of this approach in the control of CHD and other health problems on a nationwide level.

Baseline data concerning cardiovascular diseases and their main risk factors in the target community of North Karelia and in the control area of Kuopio were studied in detail. To do this, a representative random 6.6 percent sample was drawn for the 1972 population of the two communities by using the national population register. The sample comprised men and women born during 1913 to 1947 (then aged 25 to 59). About 52 percent of the men in the study were current smokers, and each smoker consumed an average of 18 cigarettes per day. Their mean levels of serum cholesterol and blood pressure were above normal, as seen in Table 4.

Owing to the high general level of the known CHD risk factors in this population, a comprehensive program was integrated into the health and social services of the community. The program consisted of (1) information given to the public, especially about the practical activities directed toward the risk factors in the community, by means of media (newspapers, radio, leaflets, posters, and stickers) and at health information education meetings and public campaigns, schools, and places of work; (2) organization of services by systematically integrating the program into existing services and creating new services when necessary, such as special supporting services for stopping smoking; (3) training personnel for the special practical tasks of the program; (4) environmental services to support the desired lifestyle, for example, with regard to smoking restrictions; and (5) internal information services to support registers for hypertension, myocardial infarction, and stroke and to help with followup surveys.

No differences were found in the prevalence of smoking between the target area and the control area at the beginning of the study in 1972. By 1977, there was a nonsignificant net reduction of 2.5 percent in the prevalence of smoking among North Karelia men relative to the control men. But when the reported amount of smoking was taken into account, a net 9.8 percent reduction was significant. This was a result of the finding that in 1972 North Karelian men smoked more than did those in the control area. There was a highly significant 4.1 percent net reduction of mean serum

TABLE 8.—Death rates and relative risk of death in those MRFIT subjects who quit at 1 year and those who continued smoking (average further followup, 6 years)

Smoking status at entry	Smoking status at year 1		CHD death rates		Total death rates	
	No. quit	No. continued	Percent quit	Percent continued	Percent quit	Percent continued
By level of smoking						
1–29 cigs/day	613	1,827	1.47	2.30	3.43	4.27
≥30 cigs/day	752	4,471	0.80	1.92	3.06	4.47
By group status						
Special intervention	991	2,842	1.11	2.04	2.93	4.68
Usual care	374	3,456	1.07	2.03	4.01	4.20
Total	1,365	6,298	1.10	2.03	3.22	4.41
Relative risk of death (quit/continued)						
By level of smoking						
1–29 cigs/day			0.64		0.80	
≥30 cigs/day			0.42		0.68	
By group status						
Special intervention			0.54		0.63	
Usual care			0.53		0.95	
Total			0.54		0.73	

cholesterol concentrations in the North Karelia men. At the start of the study, the mean serum cholesterol concentrations were higher in people in North Karelia than in the control area. There was a highly significant net reduction in systolic blood pressure from baseline for the North Karelia men. The prevalence of raised values in 1972 was similar among men in the two areas, and the net reduction in the prevalence of raised values in North Karelia was substantial and highly significant.

The estimates of CHD risk showed that in 1972 the North Karelians had a higher mean risk score than did the population in the control area. During the followup period, this difference was reversed among the men and there was a highly significant net reduction in the estimated CHD risk in North Karelia of 17.4 percent among the men. However, there were no significant relative reductions in CHD or total mortality among the North Karelia men compared with the control men as of 1977. However, a more recent analysis of mortality trends in Finland suggests that a longer period of followup may yield some significant relative reductions (*55*). Because of the different methodology used, the mortality results

TABLE 9.—Observed deaths in MRFIT and Whitehall studies and expected deaths based on general population and Framingham death rates

Study	Coronary heart disease			All causes		
	Observed in UC group	Expected (U.S. males) (1979)	SMR	Observed in UC group	Expected (U.S. males) (1979)	SMR
MRFIT study						
UC group (n=6438)						
Year						
1	9	~19	47	17	~48	35
2	20	~20	100	31	~50	62
3–6	75	~87	86	171	~223	77
7	20	~24	83	41	~63	65
1–7	124	~150	83	260	~384	68
		(Framingham)			(Framingham)	
1–7	124	~220	56	260	~515	50
UC smokers (n=4091)		(U.S. males) (1979)			(U.S. males) (1979)	
Years 1–7	89	~95	94	190	~244	78
Whitehall study		(English males)			(English males)	
NC group (n=731)		(1974)			(1974)	
Years 1–10	62	~48	129	128	~130	98

from this study have not been summarized in Tables 5 and 6, but the risk factor changes are shown in Table 4.

Comparison of Results From Intervention Trials and Epidemiologic Studies

Table 10 summarizes the expected reduction in CHD and total mortality for former smokers who stopped for 1 to 4 years or for 5 to 9 years, based on the three major observational studies in Table 1 (*10, 11, 20, 49*). This shows that, relative to current smokers, former smokers who have stopped for 1 to 9 years have a CHD mortality rate that is 25 percent less and a total mortality rate that is 18 percent less, in approximate terms. The cigarette smokers in the MRFIT and Whitehall studies have been subjected to smoking cessation intervention as the sole, or as a major, risk factor change. As seen in Table 4, smoking reduction in the intervention group relative to the control group was 31 percent in MRFIT and 54 percent in the Whitehall study, for an average reduction of about 40 percent in proportion of current smokers. This means that the expected reduction in mortality should be about 40 percent of that associated with total cessation; in other words, 10 percent for CHD mortality and 7 percent for total mortality. Combining the observed

TABLE 10.—Comparison of reductions in CHD and total mortality from observational studies of former smokers and from MRFIT and Whitehall intervention studies

	Coronary heart disease				Total mortality			
	British physicians	ACS 25-State	U.S. veterans	Average	British physicians	ACS 25-State	U.S. veterans	Average
Current smokers	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Former smokers, 1–4 yrs	.744	.613	.854	.737	.701	.934	.867	.834
Former smokers, 5–9 yrs	.887	.544	.873	.768	.861	.773	.809	.814
Average former smokers, 1–9 yrs				.753				.824
Percentage reduction, former smokers, 1–9 yrs				-24.7%				-17.6%
Percentage reduction, ~40% former smokers				-9.9%				-7.0%
	O_I	E_C		%diff(O–E)/E	O_I	E_C		%diff(O–E)/E
MRFIT smokers at S_1 (Table 7)	86	89.4		-3.7%	201	190.4		+5.6%
Whitehall smokers (Table 5)	49	60.6		-19.1%	123	125.0		-1.6%
Unweighted total	135	150.0		-10.0%	324	315.4		+2.7%
95% confidence interval				-24%→+7%				-8%→+15%

deaths from these two intervention groups shows a change in CHD mortality of −10 percent (95 percent CI from −26 percent to +6 percent) and a change in total mortality of +2.7 percent (95 percent CI from −9 percent to +14 percent). Thus, these two trials have yielded a result after 5 to 10 years of followup that is in good agreement with the observational studies for CHD deaths, but is not particularly close for total mortality. Because of the fairly large 95 percent confidence interval, the intervention results are consistent both with the observational studies and with no change at all. It must be noted that in MRFIT, other risk factor interventions took place on blood pressure and cholesterol, and interpretation of the results has raised the real possibility that an adverse effect on survival was associated with anti-hypertensive efforts in a specific subgroup of hypertensive patients, a finding which, if true, might mask a larger beneficial effect of smoking cessation.

As previously noted and as shown in Table 8, an analysis of survival in MRFIT participants who had been smokers at entry, demonstrates that those who quit at year 1 of followup had a 46 percent lower CHD mortality and a 27 percent lower all-cause mortality than those smokers who did not quit at year 1. This is further powerful evidence consistent with substantial improvement of survival associated with the cessation of cigarette smoking.

Conclusions

1. In the four intervention trials involving mortality followup of individual men for 5 to 10 years, the intervention groups had a combined total of 10 percent fewer CHD deaths than did the comparable control groups. Differences for other causes of death or for total deaths were not significant.
2. In these trials, the amount of cigarette smoking has been reduced 10 to 50 percent more in the intervention group than in the control group, demonstrating that intervention can alter smoking behavior.
3. In the two trials involving morbidity followup, the intervention groups had 4 and 45 percent lower total CHD incidence than did the respective control groups.
4. The relative reductions in CHD mortality in each of the four intervention studies involving individual followup are reasonably consistent with the reduction in CHD risk factors, and for a combination of all four studies, the reduction is statistically significant.
5. Numerous studies have shown that those who quit cigarette smoking experience a substantial decrease in CHD mortality and an improvement in life expectancy.

6. A number of prospective epidemiological studies indicate that former cigarette smokers substantially reduce their CHD and total death rates from that of current smokers.

References

(1) AUSTRALIAN NATIONAL BLOOD PRESSURE STUDY. The Australian therapeutic trial in mild hypertension. Report of the Management Committee. *Lancet* 1(8181): 1261–1267, June 14, 1980.

(2) BORHANI, N.O. Primary prevention of coronary heart disease: A critique. *American Journal of Cardiology* 40(2): 251–259, August 1977.

(3) BOSSE, R., GARVEY, A.J., COSTA, P.T., Jr. Predictors of weight change following smoking cessation. *International Journal of the Addictions* 15(7): 969–991, October 1980.

(4) CEDERLOF, R., FRIBERG, L., HRUBEC, Z., LORICH, U. *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity.* A ten year follow-up in a probability sample of 55,000 Swedish subjects age 18 to 69. Parts I and II. Stockholm, Karolinska Institute, 1975, 91 pp.

(5) COOPERATIVE RANDOMIZED CONTROL TRIAL. Control of moderately raised blood pressure. Report of a cooperative randomized controlled trial. *British Medical Journal* 3(5877): 434–436, August 25, 1973.

(6) CORONARY DRUG PROJECT RESEARCH GROUP. The Coronary Drug Project. Design, methods, and baseline results. *Circulation* 47(3, Supplement No. I): I-1—I-50, March 1973.

(7) CORONARY DRUG PROJECT RESEARCH GROUP. Clofibrate and niacin in coronary heart disease. *Journal of the American Medical Association* 231: 360–381, January 27, 1975.

(8) CORONARY DRUG PROJECT RESEARCH GROUP. Implications of findings in the Coronary Drug Project for secondary prevention trials in coronary heart disease. *Circulation* 63(6): 1342–1350, June 1981.

(9) DAYTON, S., PEARCE, M.L., HASHIMOTO, S., DIXON, W.J., TOMIYASU, U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 40(1, Supplement No. II): II-1—II-63, July 1969.

(10) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. *British Medical Journal* 1(5395): 1399–1410, May 30, 1964.

(11) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. *British Medical Journal* 1(5396): 1460–1467, June 6, 1964.

(12) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 2(6051): 1525–1536, December 25, 1976.

(13) EDERER, F., LEREN, P., TURPEINEN, O., FRANTZ, I.D., Jr. Cancer among men on cholesterol-lowering diets. Experience from five clinical trials. *Lancet* 2(7717): 203–206, July 24, 1971.

(14) ENSTROM, J.E. Trends in mortality among California physicians after giving up smoking: 1950–79. *British Medical Journal* 286: 1101–1105, April 2, 1983.

(15) FARQUHAR, J.W. The community-based model of life style intervention trials. *American Journal of Epidemiology* 108(2): 103–111, August 1978.

(16) FARQUHAR, J.W., WOOD, P.D., BREITROSE, H., HASKELL, W.L., MEYER, A.J., MACCOBY, N., ALEXANDER, J.K., BROWN, B.W., Jr., McALISTER, A.L., NASH, J.D., STERN, M.P. Community education for cardiovascular health. *Lancet* 1(8023): 1192–1195, June 4, 1977.

(17) FRIEDMAN, G.D., PETITTI, D.B., BAWOL, R.D., SIEGELAUB, A.B. Mortality in cigarette smokers and quitters. Effect of base-line differences. *New England Journal of Medicine* 304(23): 1407–1410, June 4, 1981.

(18) GORDON, T., KANNEL, W.B., McGEE, D., DAWBER, T.R. Death and coronary attacks in men after giving up cigarette smoking. A report from the Framingham study. *Lancet* 2(7893): 1345–1348, December 7, 1974.

(19) HAMILTON, M., THOMPSON, E.N., WISNIEWSKI, T.K.M. The role of blood-pressure control in preventing complications of hypertension. *Lancet* 1(7327): 235–238, February 1, 1964.

(20) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 127–204.

(21) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167–182, August 1969.

(22) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159–1172, March 8, 1958.

(23) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294–1308, March 15, 1958.

(24) HELGELAND, A. Treatment of mild hypertension: A five year controlled drug trial. The Oslo study. *American Journal of Medicine* 69(5): 725–732, November 1980.

(25) HIRAYAMA, T., HAMANO. Y. Smoking and the relationship with rates for major causes of death—An epidemiological study based upon 13 years of continued observation of 265,118 adults over 40 at 29 selected health centers throughout Japan. *Eisei no Shibyo* 28(4): 1–18, April 1981.

(26) HJERMANN, I. Smoking and diet intervention in healthy coronary high risk men. Methods and 5-year followup of risk factors in a randomized trial. The Oslo study. *Journal of the Oslo City Hospitals* 30(1): 3–17, January 1980.

(27) HJERMANN, I., VELVE BYRE, K., HOLME, I., LEREN, P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo study group of a randomised trial in healthy men. *Lancet* 2(8259): 1303–1310, December 12, 1981.

(28) HOLME, I. On the separation of the intervention effects of diet and antismoking advice on the incidence of major coronary events in coronary high risk men. The Oslo study. *Journal of the Oslo City Hospitals* 32(3/4): 31–54, March/April 1982.

(29) HUGHES, G.H., HYMOWITZ, N., OCKENE, J.K., SIMON, N., VOGT, T.M. The Multiple Risk Factor Intervention Trial (MRFIT). V. Intervention on smoking. *Preventive Medicine* 10(4): 476–500, July 1981.

(30) HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM COOPERATIVE GROUP. Five-year findings of the Hypertension Detection and Follow-up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *Journal of the American Medical Association* 242(23): 2562–2571, December 7, 1979.

(31) HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM COOPERATIVE GROUP. Five-year findings of the Hypertension Detection and Follow-up Program. II. Mortality by race, sex and age. *Journal of the American Medical Association* 242(23): 2572–2577, December 7, 1979.

(32) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8 and one-half years of observation. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases.* National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 1–125.

(33) KLEBBA, A.J., DOLMAN, A.B. Comparability of mortality statistics for the seventh and eighth revisions of the International Classification of Diseases, United States. *Vital and Health Statistics.* Series 2, Number 66. U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, DHEW Publication No. (HRA)76-1340, October 1975, 93 pp.

(34) KLEBBA, A.J., SCOTT, J.H. Estimates of selected comparability ratios based on dual coding of 1976 death certificates by the eighth and ninth revisions of the International Classification of Diseases. *Monthly Vital Statistics Report.* Vol. 28, No. 11, Supplement. U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, DHEW Publication No. (PHS)80-1120, February 29, 1980, 19 pp.

(35) KORNITZER, M., DeBACKER, G., DRAMAIX, M., KITTEL, F., THILLY, C., GRAFFAR, M., VUYLSTEEK, K. Belgium Heart Disease Prevention Project: Incidence and mortality results. *Lancet* 1(8333): 1066-1070, May 14, 1983.

(36) KORNITZER, M., DeBACKER, G., DRAMAIX, M., THILLY, C. The Belgian Heart Disease Prevention Project. Modification of the coronary risk profile in an industrial population. *Circulation* 61(1): 18-25, January 1980.

(37) KULLER, L., MEILAHN, E., TOWNSEND, M., WEINBERG, G. Control of cigarette smoking from a medical perspective. *Annual Review of Public Health* 3: 153-178, 1982.

(38) LEREN, P. The Oslo diet-heart study: Eleven-year report. *Circulation* 42(5): 935-942, November 1970.

(39) MANN, J.I., MARR, J.W. Coronary heart disease prevention: Trials of diets to control hyperlipidaemia. In: Miller, N.E., Lewis, B., (Editors). *Lipoproteins, Atherosclerosis and Coronary Heart Disease.* Volume 1. Amsterdam, Elsevier, 1981, pp. 197-210.

(40) MEDICAL RESEARCH COUNCIL RESEARCH COMMITTEE. Controlled trial of soya-bean oil in myocardial infarction. *Lancet* 2(7570): 693-700, September 28, 1968.

(41) METROPOLITAN LIFE INSURANCE COMPANY. Effects of selection on mortality. *Statistical Bulletin* 52: 9-11, June 1971.

(42) MIETTINEN, M., TURPEINEN, O., KARVONEN, M.J., ELOSUO, R., PAAVILAINEN, E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes. *Lancet* 2(7782): 835-843, October 21, 1972.

(43) MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP. Multipe Risk Factor Intervention Trial. Risk factor changes and mortality results. *Journal of the American Medical Association* 248(12): 1465-1477, September 24, 1982.

(44) NATIONAL CENTER FOR HEALTH STATISTICS. *Health, United States, 1982.* U.S. Department of Health and Human Services, Public Health Service, Health Resources Administration, National Center for Health Statistics, DHHS Publication No. (PHS)83-1232, December 1982, 191 pp.

(45) NATIONAL DIET-HEART STUDY RESEARCH GROUP. The national diet-heart study final report. *Circulation* 37(3, Supplement No. I): I-1—I-428, March 1968.

(46) NAUKKARINEN, V. *The Feasibility of Administering Preventive Treatment for Coronary Heart Disease to Middle-Aged Men.* Helsinki, Finland, K.J. Gummerus Osakeyhtioen Kirjapainossa Jyvaeskylaessae, 1981.

(47) NOPPA, H., BENGTSSON, C. Obesity in relation to smoking: A population study of women in Göteborg, Sweden. *Preventive Medicine* 9(4): 534-543, July 1980.

(48) PUSKA, P., TUOMILEHTO, J., SALONEN, J., NEITTAANMAKI, L., MAKI, J., VIRTAMO, J., NISSINEN, A., KOSKELA, K., TAKALO, T. Changes in coronary risk factors during comprehensive five-year community programme to control cardiovascular diseases (North Karelia project). *British Medical Journal* 2(6199): 1173–1178, November 10, 1979.

(49) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213–222, May-June 1980.

(50) ROSE, G., HAMILTON, P.J.S. A randomised controlled trial of the effect on middle-aged men of advice to stop smoking. *Journal of Epidemiology and Community Health* 32(4): 275–281, December 1978.

(51) ROSE, G., HAMILTON, P.J.S., COLWELL, L., SHIPLEY, M.J. A randomised controlled trial of anti-smoking advice: 10-year results. *Journal of Epidemiology and Community Health* 36(2): 102–108, June 1982.

(52) ROSE, G., HELLER, R.F., PEDOE, H.T., CHRISTIE, D.G.S. Heart disease prevention project: A randomised controlled trial in industry. *British Medical Journal* 1(6216): 747–751, March 15, 1980.

(53) ROSE, G., TUNSTALL-PEDOE, H.D., HELLER, R.F. UK Heart Disease Prevention Project: Incidence and mortality results. *Lancet* 1(8333): 1062–1066, May 14, 1983.

(54) SALONEN, J.T., PUSKA, P., KOTTKE, T.E., TUOMILEHTO, J. Changes in smoking, serum cholesterol and blood pressure levels during a community-based cardiovascular disease prevention program—The North Karelia project. *American Journal of Epidemiology* 114(1): 81–94, July 1981.

(55) SALONEN, J.T., PUSKA, P., KOTTKE, T.E., TUOMILEHTO, J., NISSINEN, A. Decline in mortality from coronary heart disease in Finland from 1969 to 1979. *British Medical Journal* 286(6381): 1857–1860, June 11, 1983.

(56) SALONEN, J.T., PUSKA, P., MUSTANIEMI, H. Changes in morbidity and mortality during comprehensive community programme to control cardiovascular diseases during 1972–7 in North Karelia. *British Medical Journal* 2(6199): 1178–1183, November 10, 1979.

(57) SELTZER, C.C. Smoking and coronary heart disease: What are we to believe? *American Heart Journal* 100(3): 275–280, September 1980.

(58) SHAPIRO, S., WEINBLATT, E., FRANK, C.W., SAGER, R.V. Incidence of coronary heart disease in a population insured for medical care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. *American Journal of Public Health* 59(Supplement 6): 1–101, June 1969.

(59) TURPEINEN, O., KARVONEN, M.J., PEKKARINEN, M., MIETTINEN, M., ELOSUO, R., PAAVILAINEN, E. Dietary prevention of coronary heart disease—The Finnish mental hospital study. *International Journal of Epidemiology* 8: 99–118, 1979.

(60) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79–50066, 1979, 1136 pp.

(61) U.S. PUBLIC HEALTH SERVICE. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service.* U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.

(62) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM)71–7513, 1971, 458 pp.

(63) VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *Journal of the American Medical Association* 213(7): 1143–1152, August 17, 1970.

(64) WERKO, L. Prevention of heart attacks. A multifactorial preventive trial in Gothenburg, Sweden. *Annals of Clinical Research* 11(2): 71–79, April 1979.

(65) WILHELMSEN, L. Risk factors for disease according to population studies in Gothenburg, Sweden. Paper presented at Skandia International Symposia, September 23–25, 1980. In: Bostrom, H., Ljungstedt, H. (Editors). *Medical Aspects of Mortality Statistics.* Stockholm, Almquist and Wiksell International, 1981, pp. 73–88.

(66) WILHELMSEN, L., TIBBLIN, G., WERKO, L. A primary preventive study in Gothenburg, Sweden. *Preventive Medicine* 1: 153–160, March 1972.

(67) WOLFF, F.W., LINDEMAN, R.D. Effects of treatment in hypertension. Results of a controlled study. *Journal of Chronic Diseases* 19: 227–240, March 1966.

(68) WORLD HEALTH ORGANIZATION EUROPEAN COLLABORATIVE GROUP. Multifactorial trial in the prevention of coronary heart disease: 2. Risk factor changes at two and four years. *European Heart Journal* 3(2): 184–190, April 1982.

(69) WORLD HEALTH ORGANIZATION EUROPEAN COLLABORATIVE GROUP. Multifactorial trial in the prevention of coronary heart disease. 3. Incidence and mortality results. *European Heart Journal,* in press.

(70) WORLD HEALTH ORGANIZATION EXPERT COMMITTEE. Prevention of coronary heart disease. *World Health Organization Technical Report Series,* Number 678, Geneva 1982, 53 pp.

APPENDIX A: TRENDS IN CARDIOVASCULAR DISEASES

Introduction and Overview

Mortality Trends

The cardiovascular diseases—primarily heart, cerebrovascular, hypertensive, and peripheral vascular diseases—are widely prevalent in our society and cause substantial illness and death. With the increasing control of infectious and parasitic diseases, especially during the first half of the 20th century, life expectancy has improved and the major cardiovascular diseases as a group have become the underlying cause of approximately 50 percent of all deaths in the United States. They are responsible for more than 950,000 deaths each year (Table 1) (*16, 27*). The economic cost of heart disease alone was estimated in 1977 to be at least $40 billion annually (*34*), and heart disease is ranked first among causes for utilization of acute care hospitals (*31*). About 21 percent of these cardiovascular deaths occur prior to age 65; 45 percent occur prior to age 75. Until recently, as the Nation's population became proportionately older, the crude death rate for the cardiovascular diseases had increased to a plateau. In contrast, the age-adjusted death rate, stable until 1940, has since declined (*2, 17, 19, 27, 40, 41*). During the 1960s, the downward trend in the age-adjusted rate steepened markedly. Almost two-thirds of the decline between 1950 and 1978 occurred after 1968, a 27 percent decline (Figure 1; Table 2) (*1, 18, 22, 23, 24, 27, 30*). Death rates for most cardiovascular diseases declined over the entire period from 1950 to 1978, except for the major subgroup of coronary heart disease (CHD), for which there was a consistent rise in mortality in the 1950s and 1960s, followed by a dramatic decline (Figure 2) (*2, 25, 27*). The age-adjusted death rate for all cardiovascular diseases combined was lower by 63 deaths per 100,000 population in 1967 than in 1950. This decrease reflected declines for cerebrovascular and hypertensive diseases that counteracted the increase of 27 deaths per 100,000 population for coronary heart disease. In the more recent period, 1968 to 1978, the death rate for all cardiovascular diseases declined by 100 deaths per 100,000 population, with declines for CHD and cerebrovascular diseases accounting for almost all of the decline. The reversal in mortality from CHD during 1968–1978 was real, although partly attributable to the shift in classification of deaths that brought more hypertensive disease deaths into the CHD classification (see the Technical Notes at the end of this appendix). It was accompanied by an acceleration in the rate of decline for mortality from the cerebrovascular diseases and a continuation of the percentage declines for other subgroups of cardiovascular diseases.

The decline in deaths from cardiovascular diseases since 1968 was striking in comparison with the trends for other causes of death. As Figure 1 and Table 2 show, the decline since 1968 for all noncardio-

TABLE 1.—Number of deaths from all causes and from the major cardiovascular diseases by age, United States, 1979

Causes of death[1] (terminology used in this report)	Total	Under 25	25–34	35–44	45–54	55–64	65–74	75–84	85 and over	Age not stated
All causes	1,913,841	113,638	47,941	57,723	135,265	286,966	449,255	493,676	328,725	652
Major cardiovascular diseases (390–488)	958,282	3,214	4,209	14,108	49,830	126,410	230,308	300,520	229,510	173
Coronary heart disease (410–414)	551,365	191	1,289	3,568	31,211	81,722	142,119	169,062	118,112	91
Acute myocardial infarction (410)	300,462	115	877	5,310	21,694	55,524	88,526	86,262	42,102	42
Other coronary heart disease (411–414)	250,903	76	412	2,258	9,517	26,198	53,593	82,800	76,010	49
Cerebrovascular diseases (430–438)	169,488	679	947	2,277	6,061	14,610	34,807	60,324	49,760	23
Hypertensive diseases (401–405)	31,916	47	210	679	2,102	4,643	7,849	9,567	6,803	16
Diseases of arterioles, capillaries (440–448	48,284	146	173	302	1,028	3,884	9,888	15,671	17,186	6
Atherosclerosis (440)	28,801	4	5	37	208	1,023	3,736	9,525	14,260	3
Aortic aneurysm (441)	14,031	43	70	127	464	1,968	4,701	4,713	1,937	2
Other (442–448)	5,452	99	98	138	356	893	1,451	1,433	989	1
All other cardiovascular (residual)	157,229	2,151	1,590	3,282	9,428	21,551	35,645	45,896	37,649	37
All other causes of death (residual)	955,559	110,424	43,732	43,615	85,435	160,556	218,947	193,156	99,215	479

[1] Coded to the *International Classification of Diseases, Ninth Revision*, World Health Organization (*45*).

SOURCE: National Center for Health Statistics (*27*).

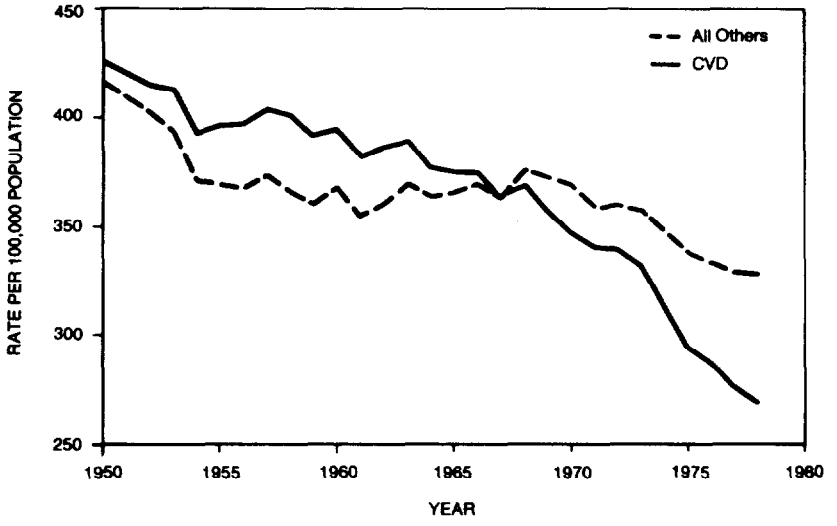


FIGURE 1.—Age-adjusted* death rates for cardiovascular diseases and all other causes of death, United States, 1950–1978

* Rates are age-adjusted to the 1940 U.S. population distribution.
SOURCE: National Center for Health Statistics (*25, 27*), Bureau of the Census (*2*).

vascular causes of death combined was only 13 percent. The decline in all cardiovascular disease deaths since 1963 translates into 289,000 fewer deaths in 1980 than would have occurred had the death rate remained at its 1970 level. The large decline for CHD alone translates into 237,000 fewer deaths in 1980 than would have occurred if the rate had remained at its peak (1963) level (see the Technical Notes at the end of this appendix). The decline in cardiovascular disease mortality, therefore, represents a major contribution to reduced total mortality and improved average life expectancy (Table 2; Figure 3) (*19, 29*).

Percentage declines were particularly steep for younger adults, for women, and for the nonwhite population, but were substantial for all demographic groups, including the elderly (Table 3). There are some geographic differences in U.S. cardiovascular mortality trends, but all areas have experienced substantial declines (*13*). Moreover, the United States differs from other countries in this decline, for in most countries the death rate continues to increase, especially for CHD among middle-aged men (Figure 4) (*46*).

TABLE 2.—Changes in the age-adjusted death rate for all causes, cardiovascular diseases, and all other causes of death, United States, 1950–1967 and 1968–1978

Cause of death	1950–1967		1968–1978	
	Change in rate per 100,000 pop.	Percent change	Change in rate per 100,000 pop.	Percent change
All causes	-115.9	-13.8	-148.8	-20.0
Total cardiovascular	-63.0	-14.8	-100.4	-27.3
Coronary heart disease	+26.6	+14.4	-64.1	-26.5
Cerebrovascular diseases	-19.1	-21.5	-26.9	-37.7
Hypertensive diseases	-33.8	60.4	-5.1	-54.3
Other arteriosclerosis	-5.1	-53.6	-3.7	-38.5
Rheumatic heart disease	-7.5	-31.5	-2.8	-38.9
Other cardiovascular diseases	-24.1	-36.8	+2.2	+7.5
All other causes of death	-52.9	-12.7	-48.4	-12.9

SOURCE: Bureau of the Census (*1*), National Center for Health Statistics (*18, 22, 23, 25, 27, 30*).

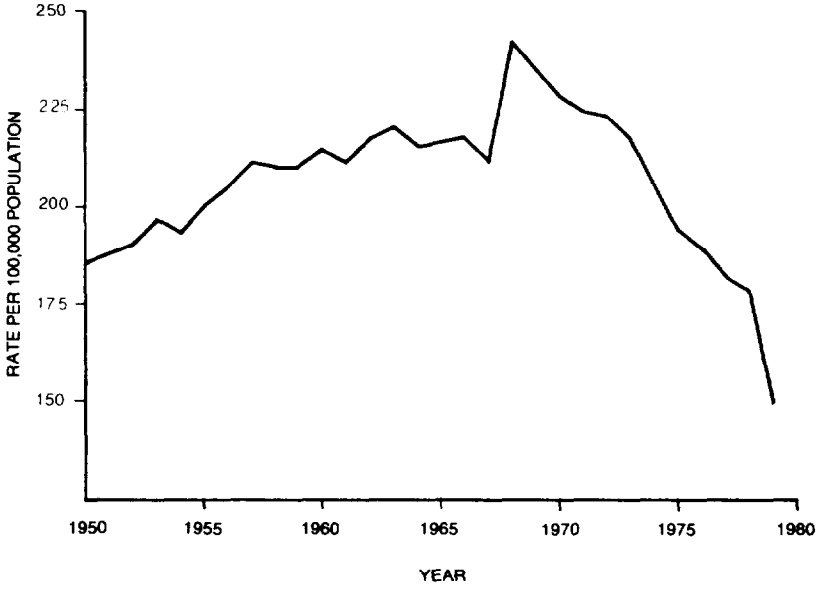


FIGURE 2.—Age-adjusted* death rates for coronary heart disease, United States, 1950–1978

* Rates are age-adjusted to the 1940 U.S. population distribution.
SOURCE: National Center for Health Statistics (25, 27), Bureau of the Census (2).

Methodological Considerations

Measurement of trends in death rates from 1950 to 1979 has been affected by (1) revisions of the International Classification of Disease in 1958, 1968, and 1979, (2) revisions of population estimates following census counts in 1960, 1970, and 1980, and (3) the major influenza epidemics in 1957, 1963, and 1968, which were years of unusually high mortality. The Technical Notes that appear at the end of this appendix discuss the International Classification of Diseases codes and explains certain adjustments, limitations, and other points of methodology of these statistics.

Cardiovascular and Noncardiovascular Mortality

The recent decline in cardiovascular mortality has not been unique. Between 1968 and 1978, the period during which the eighth revision of the International Classification of Diseases was in use, the age-adjusted death rate in the United States declined for all major causes of death except lung cancer and chronic obstructive pulmonary disease (COPD), i.e., emphysema and chronic bronchitis

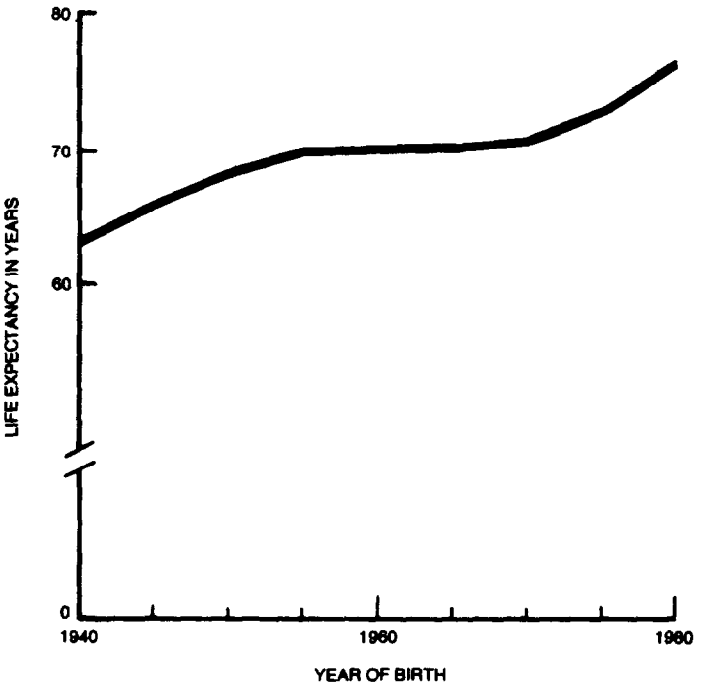


FIGURE 3.—Life expectancy at birth, United States, 1940–1980

SOURCE: National Center for Health Statistics (*19, 29*).

(Table 4). Excluding these two causes, mortality from the other causes of death declined a total of 160 deaths per 100,000 population. The percentage declines in mortality apply to both middle-aged persons and those 65 years of age or older. Although the percentage declines in mortality from diabetes mellitus and influenza or pneumonia exceed those for the cardiovascular diseases, mortality declines for the cardiovascular diseases contributed greatly to the declining overall mortality, accounting for 63 percent overall and 81 percent of the decline in mortality at age 65 and older.

Figure 5 shows that mortality rates from influenza, pneumonia, and diabetes mellitus have declined since the late 1960s. After a long-term increase, mortality from cirrhosis of the liver has declined since about 1975. Thus, the decline in cardiovascular disease mortality is not unique, but is notable for the magnitude of the decline in terms of reduced numbers of deaths and the acceleration in the declining mortality from stroke. The percentage decline in the death rates from coronary heart disease between 1969 and 1978 were

TABLE 3.—Percent changes in death rates[1] for selected causes of death by sex, color, and selected age groups, United States, 1968–1978

Color, sex, age	All causes	Cardiovascular diseases (390–458)				All other causes of death
		Total	Coronary heart diseases (410–413)	Cerebro-vascular diseases (430–438)	Other cardio-vascular diseases	
Both sexes[1]	-20.0	-27.3	-26.5	-37.7	-16.9	-12.9
25–34	-16.2	-38.8	-37.5	-46.9	-35.2	-12.9
35–44	-25.4	-35.7	-36.9	-40.6	-29.6	-21.0
45–54	-18.8	-27.2	-26.7	-38.6	-20.0	-12.6
55–64	-18.6	-27.8	-27.8	-40.3	-15.1	-9.3
65–74	-19.0	-28.1	-27.8	-40.7	-11.6	-5.9
75–84	-19.1	-25.9	-24.4	-35.5	-16.3	-4.8
85+	-21.0	-24.7	-21.1	-33.4	-24.5	-10.1
White males[1]	-17.7	-24.7	-24.5	-37.5	-11.1	-10.3
25–34	-7.5	-34.5	-31.7	-44.4	-24.2	-4.6
35–44	-22.9	-33.9	-36.4	-37.5	-19.4	-17.2
45–54	-19.4	-26.5	-27.0	-41.2	-13.4	-12.7
55–64	-19.9	-26.4	-27.0	-41.0	-10.4	-12.4
65–74	-17.1	-25.0	-24.9	-40.0	-6.3	-5.8
75–84	-13.4	-21.8	-20.0	-34.8	-9.9	+2.5
85+	-16.9	-22.9	-18.7	-34.7	-21.8	-1.9
White females[1]	-20.4	-28.3	-27.3	-36.2	-20.7	-12.7
25–34	-18.5	-38.5	-40.9	-41.7	-35.6	-15.2
35–44	-25.8	-34.1	-35.6	-34.4	-32.2	-23.4
45–54	-16.5	-27.2	-25.1	-32.9	-26.4	-12.0
55–64	-13.5	-27.3	-27.4	-35.0	-18.9	-2.9
65–74	-20.0	-30.7	-31.1	-40.3	-14.0	-4.4
75–84	-22.1	-27.7	-26.0	-35.9	-20.2	-8.9
85+	-23.2	-25.9	-22.2	-33.6	-26.9	-14.2
Nonwhite males[1]	-21.1	-27.1	-24.1	-40.0	-20.8	-16.7
25–34	-30.3	-43.1	-40.6	-52.1	-39.1	-28.5
35–44	-28.9	-38.2	-37.3	-44.8	-35.4	-25.0
45–54	-20.4	-27.2	-24.4	-41.6	-21.5	-15.6
55–64	-18.3	-28.0	-24.4	-44.8	-20.1	-8.5
65–74	-18.4	-28.4	-25.2	-40.8	-20.7	-5.1
75–84	-13.2	-21.7	-18.6	-33.5	-11.5	-0.1
85+	-7.4	-15.7	-14.5	-26.6	-3.8	+8.8
Nonwhite females[1]	-29.7	-36.0	-33.7	-45.9	-28.3	-23.8
25–34	-41.9	-58.1	-65.7	-58.4	-55.0	-37.4
35–44	-42.5	-53.9	-53.5	-60.9	-48.1	-36.8
45–54	-31.5	-42.3	-38.1	-52.4	-39.7	-23.1
55–64	-29.6	-40.0	-39.1	-51.4	-25.3	-17.7
65–74	-27.2	-36.1	-33.9	-47.7	-23.4	-11.6
75–84	-19.7	-26.6	-25.4	-34.4	-16.4	-3.9
85+	-13.3	-17.0	-13.9	-25.9	-12.6	-3.9

[1] Age-adjusted.

SOURCE: National Center for Health Statistics (27); Bureau of the Census (2).

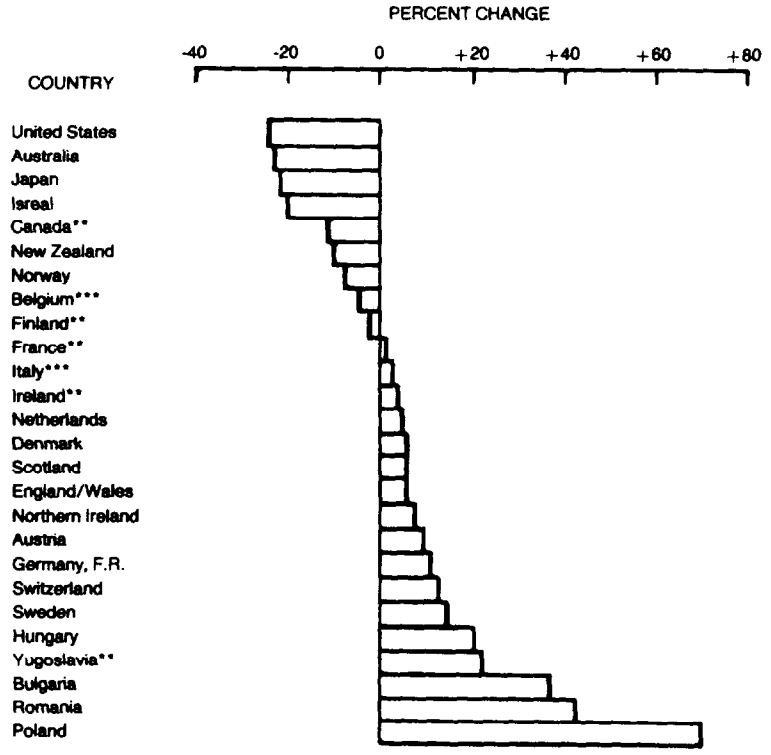


FIGURE 4.—Percent of change in the death rate for coronary heart disease in males, ages 35–74, by country, 1969–1978*

* Age-averaged rates.
** 1969–1977.
*** 1969–1976.
SOURCE: World Health Organization (*46*).

similar for the United States, Australia, Japan, and Israel (Figure 4). These percentage declines in coronary heart disease mortality among middle-aged men were at least twice the percentage decline for the noncardiovascular causes of death. The same was true for women. Elsewhere in the world, cardiovascular mortality did not decline; its percentage change was not much different from changes for the noncardiovascular causes of death as a group (*46*).

Smoking-Related Diseases

The substantial declines in cardiovascular mortality trends are a long-term pattern that can be correlated to trends in cigarette smoking in men. Before the 1950s, total mortality in the United

TABLE 4.—Change in age-adjusted death rates for all ages and two age groups by cause of death, United States, 1968–1978

Cause of death	All ages				Ages 25–64				Ages 65+			
	Rate/100,000			Percent	Rate/100,000			Percent	Rate/100,000			Percent
	1968	1978	Change	change	1968	1978	Change	change	1968	1978	Change	change
All causes	743.8	595.0	-148.8	-20.0	591.4	476.3	-115.1	-19.5	5,519.6	4,453.0	-1066.6	-19.3
Coronary heart disease	241.6	177.5	-64.1	-26.5	168.5	120.6	-47.9	-28.4	2,297.4	1,711.6	-585.8	-25.5
Cerebrovascular diseases	71.3	44.4	-26.9	-37.7	36.3	21.7	-14.6	-40.2	768.4	483.3	-285.1	-37.1
Other cardiovascular	55.5	46.1	-9.4	-16.9	41.0	32.8	-8.2	-20.0	493.4	414.7	-78.7	-16.0
Lung cancer	24.9	33.2	+8.3	+33.3	29.0	37.0	+8.0	+27.6	152.3	214.4	+62.1	+40.8
Other cancer	104.3	98.4	-5.9	-5.6	103.3	94.4	-8.9	-8.6	723.4	716.4	-7.0	-1.0
COPD	11.6	14.5	+2.9	+25.0	8.8	9.1	+0.3	+3.4	103.2	143.6	+40.4	+39.1
Influenza and pneumonia	26.9	15.1	-11.8	-43.9	15.3	8.0	-7.3	-47.7	205.7	143.8	-61.9	-30.1
Diabetes mellitus	14.6	10.2	-4.4	-30.1	11.6	8.1	-3.5	-30.2	126.0	88.7	-37.3	-29.6
Cirrhosis of the liver	13.9	12.4	-1.5	-10.8	22.5	19.6	-2.9	-12.9	36.9	37.3	+0.4	+1.1
Accidents, poisonings, and violence	76.5	66.7	-9.8	-12.8	84.7	73.6	-11.1	-13.1	158.6	111.2	-47.4	-29.9
All other causes	102.7	76.5	-26.2	-25.5	70.4	51.4	-19.0	-27.0	454.3	388.0	-66.3	-14.6

SOURCE: National Center for Health Statistics (27), Bureau of the Census (2).

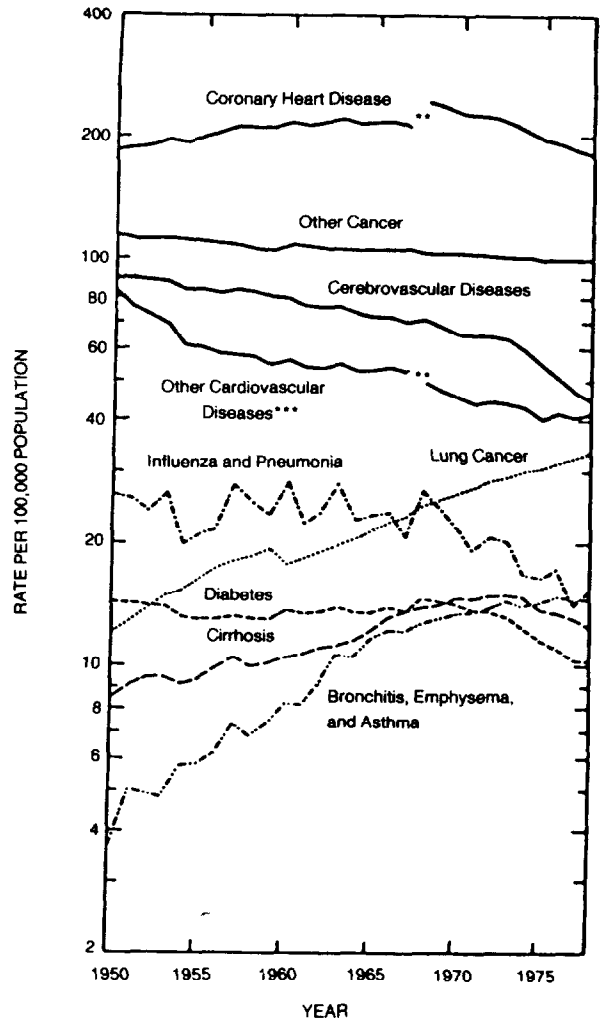


FIGURE 5.—Age-adjusted* death rates for the leading causes of death, United States, 1950–1978

* Rates are age-adjusted to the 1940 U.S. population distribution.

** This break in trend is due to a revision of the International Classification of Diseases. It affects the cardiovascular diseases more than other causes of death.

*** Primarily hypertensive, peripheral, and rheumatic heart disease.

SOURCE: National Center for Health Statistics (*18, 22, 23, 27, 30*), Bureau of the Census (*1, 2*).

States declined rapidly, as the decreased mortality from infectious and parasitic diseases masked an increasing mortality rate from diseases associated with smoking—especially CHD, lung cancer, and COPD. Between 1955 and 1965, the total mortality decline stopped for men and slowed for women, partly because the numbers of deaths

from the smoking-related diseases of lung cancer, chronic obstructive lung disease, and cardiovascular disease were increasing quite substantially (especially among men), cancelling the gains made in other causes of death. Percentage increases were greater for lung cancer and COPD than for CHD, but compared with rates for CHD, death rates for these two diseases were lower in absolute terms. Since the mid-1960s, the remarkable decline in the coronary death rate has resulted in a new decline in total mortality. Although death rates for lung cancer and COPD are still increasing, the rate of increase is slowing, and in recent years, there is a suggestion of a reversal in lung cancer mortality among the younger cohorts (*39*).

Coronary Heart Disease Mortality

The age-adjusted death rate for CHD increased 19 percent from 1950 to 1963, peaked in 1963, and then declined 30 percent from 1963 to 1979 (Figure 2). (This assumes good comparability of cause-of-death assignment and classification to CHD for 1963 and 1979. See the Technical Notes at the end of this appendix.) The reversal of the trend was gradual; however, the inflection point was the mid-1960s. During the period between 1968 and 1978, when CHD mortality was classified according to the eighth revision of the International Classification of Diseases, the age-adjusted death rate declined 26.5 percent (Table 3). The decline was greatest at younger ages, ranging from 38 percent for ages 25 to 34 to 21 percent for age 85 and older. Nonwhite females experienced the largest decline of any sex/color group—34 percent, with declines exceeding 50 percent in persons 45 years of age or younger. The mortality trends for CHD displayed in Figure 6 show a striking change from the differential trends among the four sex/color groups prior to 1968 and remarkably similar downward slopes since then. Rates for white and nonwhite females appear to have begun their current decline in about 1964. The earliest that the rates for white and nonwhite males began their current decline was 1967, following a brief plateau. Further, age-specific CHD mortality trends prior to the current decline showed greater differences than during the current decline (Figure 7). As stated above, however, declines continue to be steeper for younger than for older persons. The decline in CHD mortality is substantial in every State in the country, but is less marked in Appalachia, an area of relatively high CHD mortality. There is also some evidence that for life insurance policyholders, constituting a higher socioeconomic group than the general population, declines are steeper than for the general population (*15*).

A breakdown of CHD deaths into deaths from acute myocardial infarction and deaths from other types of CHD is possible, but it is not known to which group most sudden or out-of-hospital CHD

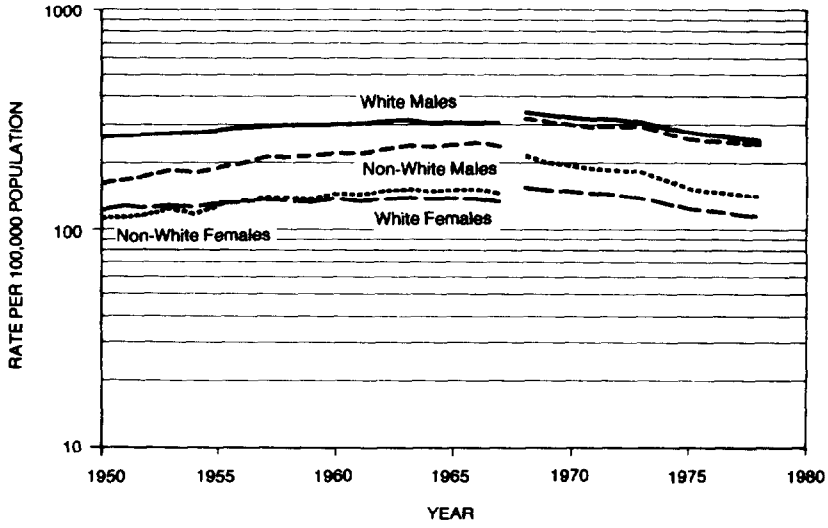


FIGURE 6.—Age-adjusted* death rates for coronary heart disease by sex and color, all ages, United States, 1950–1978

* Rates are age-adjusted to the 1940 U.S. population distribution.
SOURCE: National Center for Health Statistics (*25, 27*), Bureau of the Census (*2*).

deaths are classified (Table 1). A much steeper decline in the death rate for acute myocardial infarction than for other CHD occurred during the 1968–1978 period (Figure 8). More information is needed before it can be determined what significance to ascribe to this difference.

Other Cardiovascular Disease Mortality

The leading cause of death after heart disease and cancer is stroke, a cerebrovascular disease and a major component of cardiovascular diseases. The underlying process for about 80 percent of all strokes is arteriosclerosis, and hypertension is a major contributing factor (*38*). However, the age-adjusted death rate for stroke has been declining since before 1930, and has shown an accelerated downward trend in recent years (Figure 9). In the time period 1950–1967, the age-adjusted death rate for cerebrovascular disease declined almost 22 percent; this rate of decline accelerated during the time period 1968–1978 to 38 percent (Table 2). The death rate declined 1.0 percent per year in the 1950s and 1.8 percent per year in the 1960s. As is the case for CHD, the trend for stroke mortality since 1968 has been

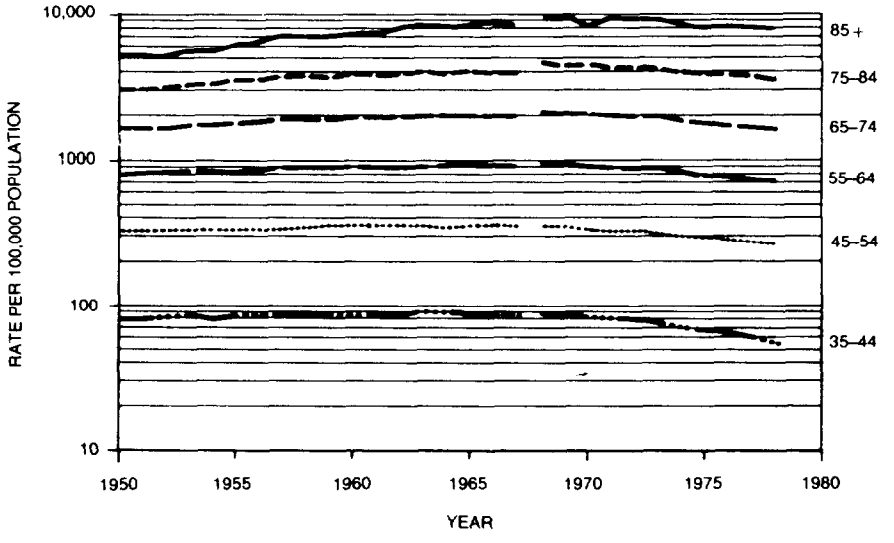


FIGURE 7.—Age-adjusted* death rates for coronary heart disease by age, white males, United States, 1950–1978

* Rates are age-adjusted to the 1940 U.S. population distribution.
SOURCE: National Center for Health Statistics (*25, 27*), Bureau of the Census (*2*).

uniformly downward for the sex/color groups, with declines being especially steep for nonwhites and younger adults (*2, 21, 23, 27*).

The age-adjusted death rate for hypertensive disease declined an average of 4.9 percent per year in the 1950s, 5.0 percent between 1960 and 1967, and 7.2 percent between 1970 and 1978. Similar to the trend for stroke, there is a steepening of the long-term decline in mortality from hypertensive disease, with recent declines being steeper among nonwhites than among whites. Large declines for the general arteriosclerosis category and for all other cardiovascular diseases combined occurred throughout the 1950–1978 period, including a decline in mortality rates for aortic aneurysm from 1968 to 1978.

Incidence and Case-Fatality

A decline in mortality rates may reflect changes in either the number of new and recurrent coronary attacks (incidence) or the survivorship from such attacks (case-fatality). Reliable national statistics of either incidence or case-fatality are not available. National prevalence and hospital discharge statistics are limited as

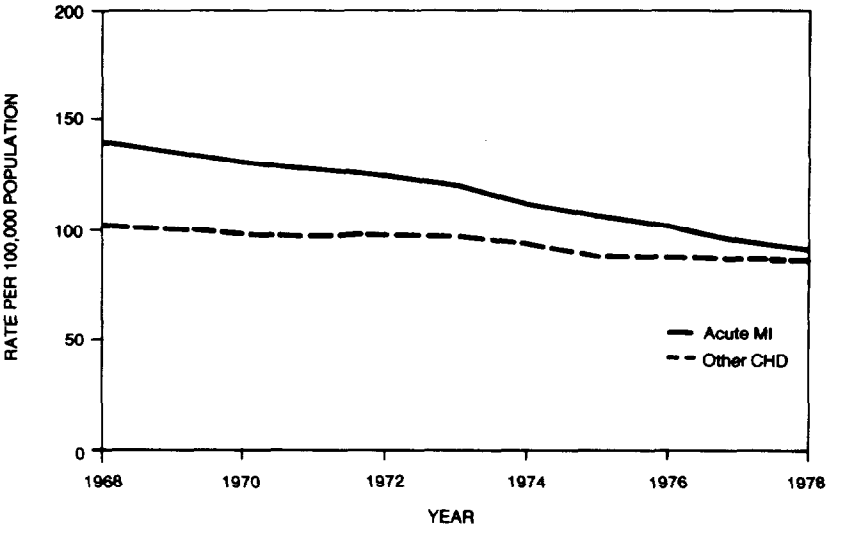


FIGURE 8.—Age-adjusted* death rates for acute myocardial infarction and other CHD, United States, 1968–1978

* Rates are age-adjusted to 1940 U.S. population distribution.
SOURCE: National Center for Health Statistics (*27*), Bureau of the Census (*2*).

measures of these trends. Reliance therefore must be placed primarily on available community- or hospital-based studies.

In a study of male employees of the DuPont company in Delaware, the incidence rate of acute myocardial infarction was 18 percent lower in the 1973–1979 period than in the 1957–1964 period (*33*). Overall 30-day case-fatality rates and the proportion of sudden deaths did not change significantly. However, beginning about 1969, the 30-day mortality among persons who survived 24 hours after the attack declined significantly.

In the Kaiser-Permanente Medical Care Program in the San Francisco area, the proportion of persons hospitalized each year (rate/1,000 subscribers) for acute myocardial infarction declined 27 percent between 1971 and 1977 (*5*). The proportion of persons hospitalized for any coronary heart disease event declined 18 percent. The decline was seen in both first and recurrent events and did not result from shifting to noncoronary diagnoses. No clear trend could be ascertained in the proportion of persons who died from acute myocardial infarction of all persons hospitalized for this disease each year.

In a study of the population of Rochester, Minnesota, there was no change in the incidence of initial manifestations of coronary heart

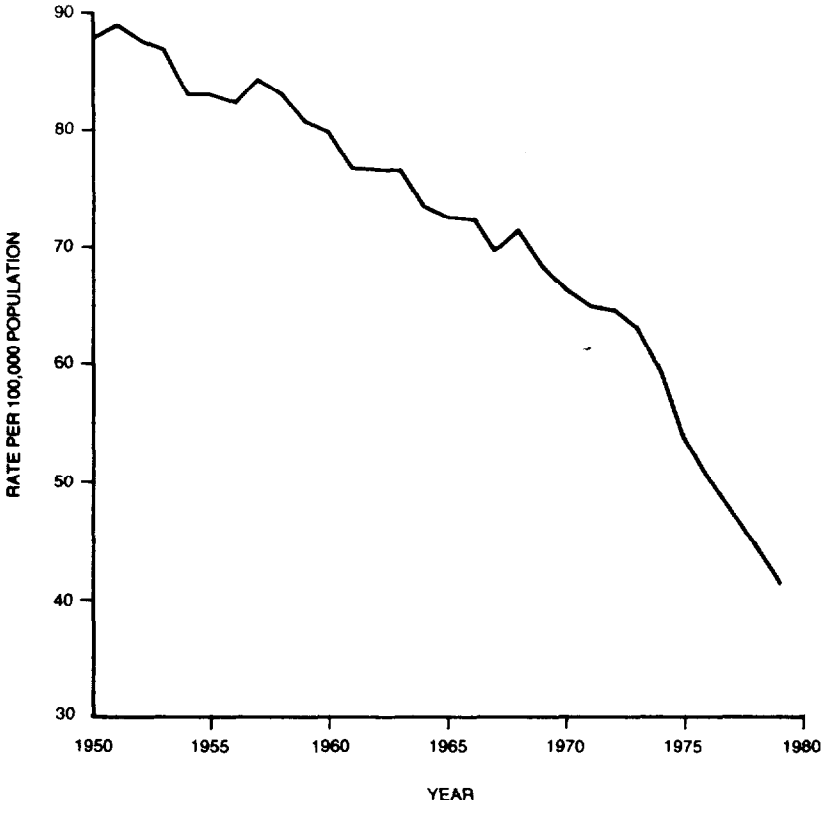


FIGURE 9.—Age-adjusted* death rates for cerebrovascular diseases, all ages, United States, 1950–1978

* Rates are age-adjusted to the 1940 U.S. population distribution.
SOURCE: National Center for Health Statistics (*21, 23, 27*), Bureau of the Census (*2*).

disease between 1950 and 1969 (*3*). However, the case-fatality rate, based on sudden, unexpected deaths and myocardial infarction deaths under 30 days, was 34 percent in the 1970–1975 period, whereas it had been 47 percent in the 1950–1955 period. In contrast, during 1971–1978, males under 65 years of age enrolled in the Health Insurance Plan of Greater New York who had recovered from a first myocardial infarction showed no better survival over 4.5 years than did a comparable group during 1961–1970 (*43*).

One study provides secular trends on the severity of coronary atherosclerosis between 1960–1964 and 1968–1972 (*36*). Autopsy findings in this New Orleans study reveal that the extent of intimal surface covered by raised lesions decreased significantly between

1960–1964 and 1968–1972 among white males 25 to 44 years of age, and also decreased slightly among black males.

In the Kaiser-Permanente study, the proportion of persons hospitalized for cerebral thrombosis dropped 64 percent between 1971 and 1977, most of the drop occurring after 1973. The decline for all cerebrovascular diseases combined was 15 percent. In the Rochester, Minnesota, population there was a 45 percent decline in the incidence of stroke between 1945 and 1974, with reductions more pronounced in the elderly (*6*). The Framingham study observed a lower incidence rate for stroke among women (but not among men) followed since 1962, as compared with women followed since 1950 (*10*).

Trends in national hospital discharge statistics from the National Center for Health Statistics are available, but difficult to interpret. Discharge rates for both acute myocardial infarction and stroke between 1970 and 1978 show no increase in incidence of acute events (Figure 10) (*26, 37*). These data, however, are not inconsistent with a decline in CHD incidence, because patients are increasingly being admitted for cardiac pacemaker insertion and replacement, for catheterizations, and for other diagnostic and therapeutic procedures (Table 5). Figure 11 shows annual data on hospital case-fatality rates. Despite annual fluctuations, the trend in case-fatality rates from 1970 to 1978 is clearly downward for acute myocardial infarction. This could result from an increased tendency to admit milder cases not previously hospitalized, from a real improvement in therapeutic efficacy, or from a mixture of both.

Risk Factors and Treatment

Risk Factor Reduction

As is discussed elsewhere in this Report, three major modifiable risk factors—cigarette smoking, hypertension, and hypercholesterolemia—are statistically significant contributors to cardiovascular risk for both men and women (Table 10) (*14*). Cigarette smoking, hypertension, and a high serum cholesterol each have been found to increase coronary heart disease risk. The nationwide efforts to reduce cigarette smoking, to control high blood pressure, and to avoid foods high in saturated fats (*4*) have reduced the levels of these risk factors during the past 15 years (Tables 6, 7, 8, and 9) (*24, 28, 32*). The reduction in each of the risk factors coincides with the observed decline in CHD mortality.

Attempts have been made to estimate how much of the reduction in cardiovascular disease mortality can be ascribed to observed reductions in risk factor levels (*11, 12, 35*). Findings have not been definitive because of data limitations. It has not been possible to quantify or to rank the separate contributions of a reduction in any

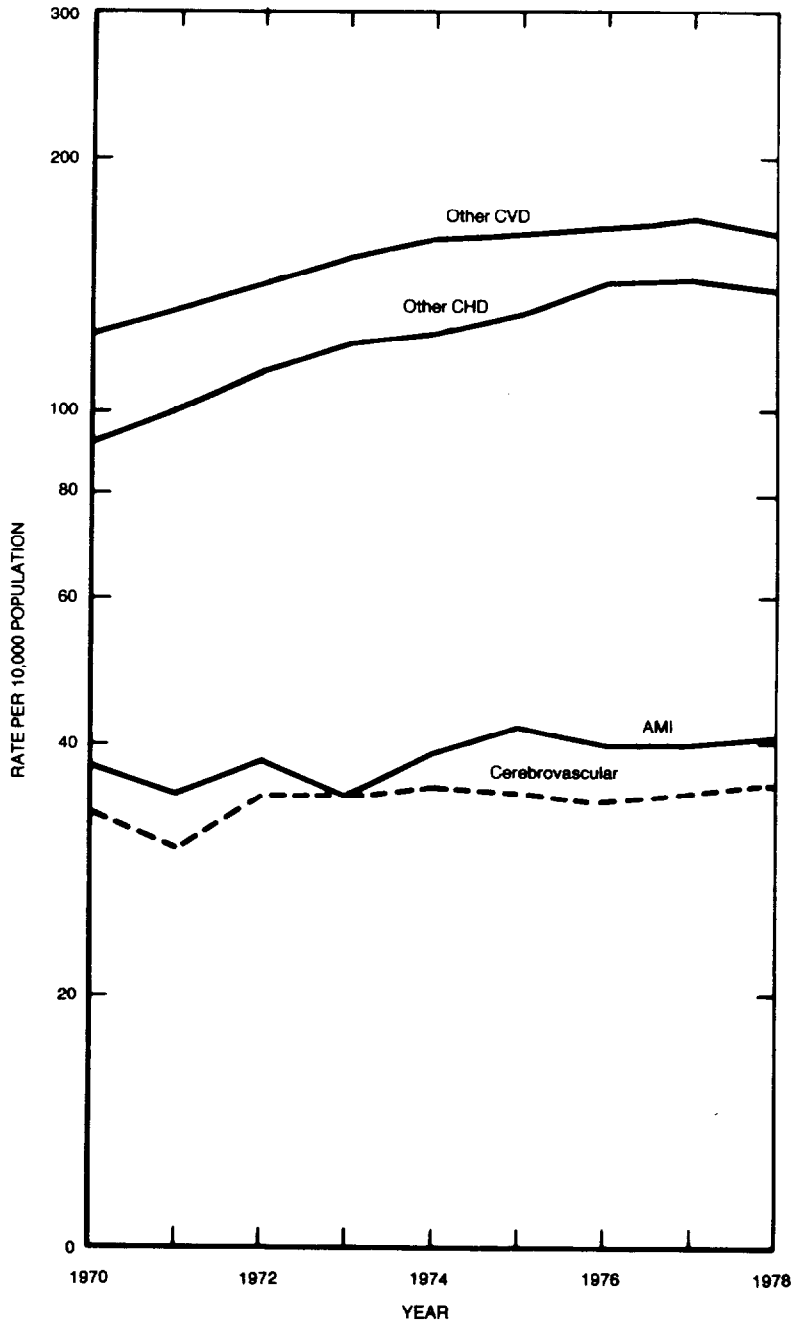


FIGURE 10.—Rate of hospital discharges for major components of cardiovascular disease, ages 45–65, United States, 1970–1978

SOURCE: National Center for Health Statistics (*26*), Thom et al. (*37*).

TABLE 5.—Number of selected cardiovascular surgical procedures, United States, 1970, 1975, 1980

Procedure	1970	1975	1980
Coronary bypass[1]	14,000	57,000	137,000
Cardiac valves[2]	16,000	23,000	35,000
Catheterizations[3]	77,000	189,000	348,000
Pacemaker insertions[4,5]	24,000	60,000	143,000
All vascular and cardiac[6]	506,000	888,000	1,484,000

[1] ICD/8 codes 29.8; ICD/9 codes 36.1–36.3.
[2] ICD/8 codes 29.2–29.4; ICD/9 codes 35.1,35.2,35.99.
[3] ICD/8 codes 30.2; ICD/9 codes 37.21–37.23.
[4] ICD/8 codes 30.4; ICD/9 codes 37.7.
[5] ICD/8 codes 24–30; ICD/9 codes 35.1–40.5.
[6] Excludes replacements.
SOURCE: National Center for Health Statistics (26), Thom (37).

one risk factor to the mortality decline, but one analysis concluded that "elimination of smoking would have the greatest impact on CHD death rates" (*11*). The extent to which changes in these risk factors may have contributed to the decline in mortality depends, in part, on their prevalence in the U.S. population, and thus, on the reduction in prevalence that has taken place in recent years.

An estimated 38.3 percent of adult men and 29.2 percent of adult women smoke cigarettes, that is, 50 to 55 million persons as of 1980 (Table 6). These percentages represent large declines from the 52.4 percent and 34.1 percent, respectively, in 1965 (*28*). Table 6 gives the age-adjusted and age-specific rates that correspond to these crude rates of smoking. In a 1976 to 1980 survey, an estimated 22 percent of persons 25 to 74 years of age, about 25 million persons, had hypertension, i.e., a systolic blood pressure of 160 mm Hg or greater, a diastolic blood pressure of 95 mm Hg or greater, or were on antihypertensive medication (Table 8) (*32*). Although the prevalence rate in 1960–1962 was about the same (20 percent), a much larger proportion of persons with hypertension in the more recent period were aware of it (73 vs. 49 percent), were on treatment for it (56 vs. 31 percent), and had it controlled (34 vs. 16 percent). In a survey in 1971–1974, an estimated 21.9 percent of persons 18 to 74 years of age, 28 million persons, had serum cholesterol levels of 260 mg/100 ml or greater (*24*). After adjusting these crude rates to make them comparable by age to estimates in the 1960–1962 survey, the percentage of persons at that level or greater was less than in the 1960–1962 survey, although the decline was not statistically significant for all age/sex groups (Table 9). As of 1979, there were about 5 million adults with diabetes mellitus, 3 percent of the adult population (*28*). There apparently has been no reduction in prevalence in recent years.

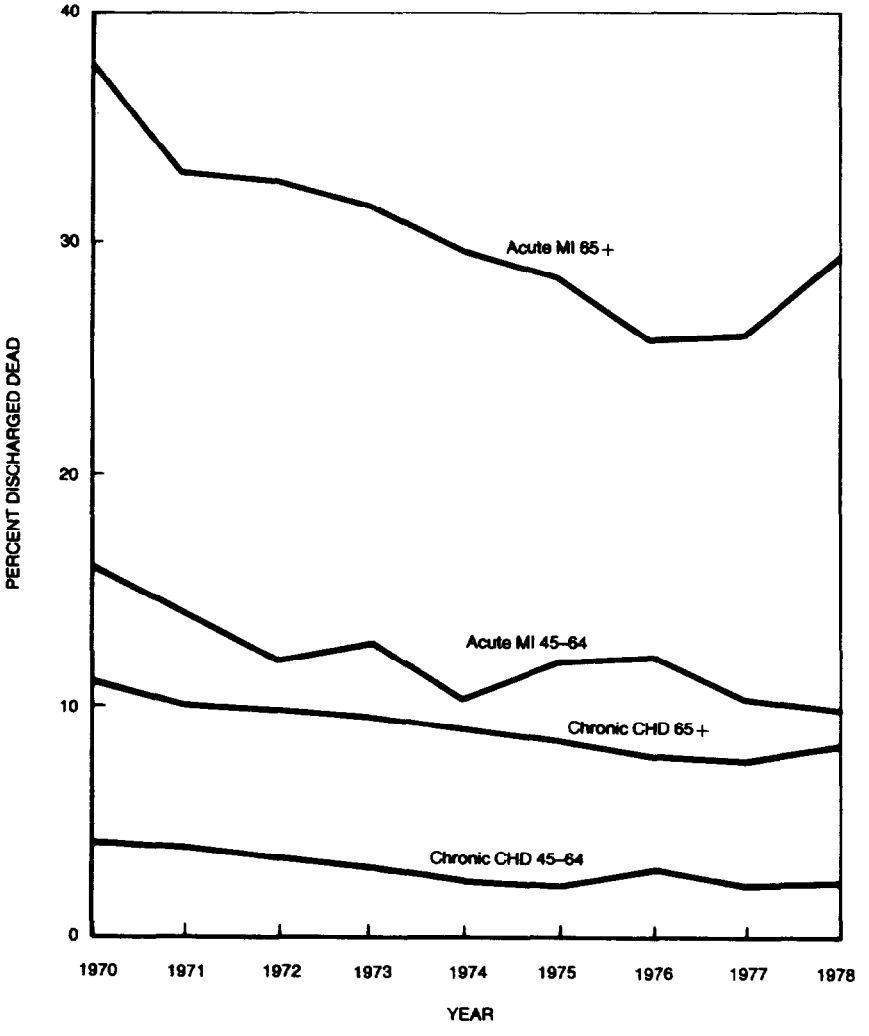


FIGURE 11.—Hospital case-fatality rate for acute myocardial infarction and chronic CHD, United States, 1970–1978

NOTE: First listed diagnosis on discharge: ICD/8 code 410 for acute MI, and 412 for chronic CHD.
SOURCE: National Center for Health Statistics (26), Thom et al. (37).

The correlation of independent risk factors to cardiovascular disease risk is shown in Table 10. The documented changes in risk factors in Tables 6–9 suggest that the decline in the prevalence of cigarette smoking, which affected the greatest number of people, may have contributed more to the decline than did changes in the other risk factors. This assertion depends on the quality of data on

the prevalence of smoking, the changes in prevalence of smoking, and the relative strength of the association between smoking and CHD risk, as well as evidence that cessation of smoking lowers the risk of acute and recurrent myocardial infarction mortality.

Impact of Improved Treatment

Improvements have been made in recent years in the medical care of the coronary patient prior to, during, and after hospitalization. Treatment is now more aggressive and sophisticated, and the improved management techniques are more generally available throughout the country. Today's coronary patient has a much better chance of arriving alive at a hospital and at an earlier stage of the episode than was the case a decade or two ago (*7*). Once hospitalized, the patient is monitored for arrhythmias and changes in cardiac function, usually in a coronary care unit. Catheterizations and coronary artery bypass surgery have been performed with greatly increased frequency in recent years (Table 5). It is likely that improved treatment in a hospital has reduced the case-fatality rate of these patients (Figure 11). The post-discharge treatment is better managed today. The coronary patient with angina pectoris or hypertension receives more aggressive and effective treatment; antiarrhythmic drug therapies are widely used; and many patients are advised to stop smoking, modify their diet, and lose weight. Although documentation of the occurrence in time of many of these treatment improvements is incomplete, most were made in the 1960s and 1970s.

Trends and Associated Factors

The reversal of the death rate for CHD and the acceleration of the decline for stroke have coincided over time with increased efforts in primary and secondary prevention. These efforts include the anti-smoking campaigns since 1964, the nationwide campaign against hypertension since 1972, a trend away from saturated fats in the diet, and changes in treatment, such as expanded utilization of coronary care units, cardiac surgery, cardiac catheterization, and pacemakers (*8*). The public is now more aware of cardiovascular risk factors, especially cigarette smoking, hypertension, and elevated serum cholesterol. Also, when a heart attack or stroke occurs, today's patient generally receives more aggressive medical management (*7, 9*).

Trends and Smoking

The proportion of both cigarette smokers and CHD mortality increased until the mid-1960s and then declined markedly. Tempo-

TABLE 6.—Percentage distribution of adult current and former cigarette smokers, according to sex, race, and age, in 1965, 1976, and 1980

Sex, race, and age	Current smoker[1] (percent)			Former smoker (percent)		
	1965	1976	1980[2]	1965	1976	1980[2]
MALE						
Total[3,4]						
All ages ≥ 20[5]	52.1	41.6	37.9	20.3	29.6	30.5
20–24	59.2	45.9	39.7	9.0	12.2	12.1
25–34	60.7	48.5	43.1	14.7	18.3	20.6
35–44	58.2	47.6	42.6	20.6	27.3	27.6
45–64	51.9	41.3	40.8	24.1	37.1	36.9
≥ 65	28.5	23.0	17.9	28.1	44.4	47.4
White						
All ages ≥ 20[5]	51.3	41.0	37.1	21.2	30.7	31.9
20–24	58.1	45.3	39.0	9.6	13.3	12.2
25–34	60.1	47.7	42.0	15.5	18.9	21.9
35–44	57.3	46.8	42.4	21.5	28.9	28.8
45–64	51.3	40.6	40.0	25.1	38.1	38.4
≥ 65	27.7	22.8	16.6	28.7	45.6	50.1
Black						
All ages ≥ 20[5]	59.6	50.1	44.9	12.6	20.2	20.6
20–24	67.4	52.8	45.5	3.8	4.1	10.6
25–34	68.4	59.4	52.0	6.7	11.8	11.9
35–44	67.3	58.8	44.2	12.3	13.8	21.2
45–64	57.9	49.7	48.8	15.3	28.6	26.3
≥ 65	36.4	26.4	27.9	21.5	33.0	26.6
FEMALE						
Total[3,4]						
All ages ≥ 20[5]	34.2	32.5	29.8	8.2	13.9	15.7
20–24	41.9	34.2	32.7	7.3	10.4	11.0
25–34	43.7	37.5	31.6	9.9	12.9	14.4
35–44	43.7	38.2	34.9	9.6	15.8	18.9
45–64	32.0	34.8	30.8	8.6	15.9	17.1
≥ 65	9.6	12.8	16.8	4.5	11.7	14.2
White						
All ages ≥ 20[5]	34.5	32.4	30.0	8.5	14.6	16.3
20–24	41.9	34.4	33.3	8.0	11.4	12.5
25–34	43.4	37.1	31.6	10.3	13.7	14.7
35–44	43.9	38.1	35.6	9.9	17.0	20.2
45–64	32.7	34.7	30.6	8.8	16.4	17.4
≥ 65	9.8	13.2	17.4	4.5	11.5	14.3
Black						
All ages ≥ 20[5]	32.7	34.7	30.6	5.9	10.2	11.8
20–24	44.2	34.9	32.3	2.5	5.0	2.2
25–34	47.8	42.5	34.2	6.7	8.9	11.6
35–44	42.8	41.3	36.5	7.0	9.6	12.5
45–64	25.7	38.1	34.3	6.6	11.9	14.1
≥ 65	7.1	9.2	9.4	4.5	13.3	14.1

[1] A current smoker has smoked at least 100 cigarettes and now smokes; includes occasional smokers.

[2] Final estimates. Based on data for the last 6 months of 1980.

[3] Base of percentage excludes persons with unknown smoking status.

[4] Includes all other races not shown separately.

[5] Age adjusted by the direct method to the 1970 civilian noninstitutionalized population using 5 age groups.

NOTE: Percentages do not add up to 100 because of "never smokers" in the survey population.

SOURCE: Data from the National Health Interview Survey, National Center for Health Statistics, 1965, 1976, and 1980, based on household interviews with a sample of the civilian noninstitutionalized population.

rally, the beginning of the decline in CHD mortality closely followed the decline in prevalence of smoking after the issuance of the first

TABLE 7.—Change in percentage of current cigarette smokers and of those who smoke 25 or more cigarettes per day, by color, sex, and age, United States, 1965 to 1980

Color, sex, and age	All current smokers	Smoke 25 or more cigarettes per day
White men, age 20+	-27.0	+0.7
20–24	-31.8	-9.2
25–34	-30.6	-12.1
35–44	-26.5	-2.1
45–64	-21.6	+18.2
65 and older	-37.5	+14.3
Black men, age 20+	-25.8	-12.5
20–24	-29.4	-11.1
25–34	-23.1	-24.2
35–44	-37.6	-32.1
45–64	-19.7	+22.2
65 and older	-20.6	+166.7
White women, age 20+	-13.7	+46.2
20–24	-21.2	+38.6
25–34	-27.2	+16.7
35–44	-18.9	+55.6
45–64	-7.6	+66.0
65 and older	+78.6	+257.1
Black women, age 20+	-14.0	+50.0
20–24	-28.7	unknown[1]
25–34	-31.2	+26.2
35–44	-19.6	+15.4[1]
45–64	-31.1	+344.4[1]
65 and older	+22.5	unknown[1]

[1] Figure does not meet standards of reliability or precision.
SOURCE: National Center for Health Statistics (*25*).

Report of the Surgeon General on *The Health Consequences of Smoking.* The same phenomenon has been reported in other countries as well (*37*).

The decline for CHD mortality is occurring among adults of all age, color, and sex groups, a pattern similar to that of the reduction in the proportion of the population who are cigarette smokers. The mortality decline is steeper among younger adult age groups, which is consistent with not starting to smoke or early smoking cessation. Since 1950 for males and 1960 for females, each succeeding sex cohort has experienced a lower peak prevalence of smoking (*42*). The evidence of more rapid declines in mortality for persons on a higher

TABLE 8.—Prevalence, awareness, and control rates of hypertension, persons 25–74 years of age, United States, 1960–1962, 1974–1975, 1976–1980[1]

Year	Percentage of population with hypertension[2]	Percentage of total with hypertension			
		Unaware[3]	Aware, no medication	Aware, medication, no control	Aware,[4] medication, controlled
1960–1962	20.3	51.1	17.6	15.3	16.0
1974–1975	22.1	36.4	29.4	14.6	19.6
1976–1980	22.0	26.6	17.2	22.1	34.1

[1] Rates age-adjusted by the direct method to the population at the midpoint of the 1976–1980 National Health and Nutrition Examination Survey.

[2] Systolic blood pressure 160 mm Hg or greater, or diastolic blood pressure 95 mm Hg or greater, or on antihypertensive medication.

[3] Reported never told by physician of having hypertension.

[4] Those with hypertension taking antihypertensive medication whose blood pressure was not hypertensive.

SOURCE: National Center for Health Statistics (*32*).

TABLE 9.—Percentage of adults with serum cholesterol levels of 260 mg/100 ml and over, by sex and age, United States, Health Examination Survey (HES) 1960–1962 and Health and Nutrition Examination Survey (HANES) 1971–1974[1]

Age	HES, 1960–1962		HANES, 1971–1974	
	Men	Women	Men	Women
	Percentage			
Total, age 18–74	17.6	22.7	14.7	17.5
18–24	3.9	4.6	2.8	3.0
25–34	10.4	7.4	8.2	5.6
35–44	20.2	12.9	17.1	9.6
45–54	25.7	28.0	24.1	24.6
55–64	23.5	49.7	20.2	35.3
65–74	21.6	51.0	20.9	40.7

[1] Age adjusted by the direct method to 1971–1974 civilian noninstitutionalized population.

NOTE: All cholesterol values have been adjusted to approximate the values of Abell et al. (Abell, L.L., Levy, G.B., Brodie, B.B., Kendall, F.E. A simplified method for the estimation of total cholesterol in serum, and demonstration of its specificity. *Journal of Biological Chemistry* 195: 357–366, 1952), the common referenced method, by reducing the 1960–1962 data by 7.6 percent and the 1971–1974 data by 4.5 percent.

SOURCE: National Center for Health Statistics (*24*).

socioeconomic level and lesser declines in poorer areas of the country are also consistent with a favorable impact of smoking prevention or cessation efforts on CHD mortality, in view of the clearly demonstrated inverse relationship of male income level and prevalence of smoking.

TABLE 10.—Regression coefficients, risk ratios, and statistical significance for the risk of cardiovascular disease in 8 years, men and women, age 35–74 years, Framingham heart study

Risk factor	Multiple regression coefficient[1]	T[2]	Risk ratios evaluated at age 55[3]	
			Risk ratio	Risk factor difference
	MEN			
Cigarette smoking	0.580	6.48	1.8	Smoker/nonsmoker
Serum cholesterol	0.020	3.65	1.3	42 mg/dl
Cholesterol/age interaction	-0.001	-2.61	—	—
Systolic blood pressure	0.017	9.12	1.4	20 mm Hg
Glucose intolerance	0.410	2.92	1.5	Present/absent
	WOMEN			
Cigarette smoking	0.233	2.37	1.3	Smoker/nonsmoker
Serum cholesterol	0.019	2.98	1.2	46 mg/dl
Cholesterol/age interaction	-0.001	-2.77	—	—
Systolic blood pressure	0.015	8.59	1.4	24 mm Hg
Glucose intolerance	0.757	5.40	2.1	Present/absent

[1] Unstandardized coefficient of the multiple risk function for cardiovascular disease within 8 years with the independent variables being serum cholesterol, cholesterol times age, systolic blood pressure, cigarette smoking, glucose intolerance, left ventricular hypertrophy on ECG, age, and age squared; estimated over the age range 35–74 years.

[2] These risk factors are statistically significant for both men and women. The critical value of T is approximately equal to 2.0 at $\alpha = 0.05$.

[3] The hypothetical risk of development of cardiovascular disease associated with the specified difference in risk factor levels when other risk factors in the model are held constant. A ratio greater than 1 represents positive association with cardiovascular disease. For serum cholesterol and systolic blood pressure, the difference chosen was one standard deviation of the measurement.

SOURCE: McGee and Abbott (*14*).

Some questions remain unanswered regarding the contribution of smoking cessation to the decline in CHD mortality. The percentage of smokers who are heavy smokers appears to be increasing, although it is not known whether this represents a greater cessation rate among lighter smokers than among heavier smokers. The percentage decline in CHD mortality for women has been as large as for men, although proportionately fewer women than men have given up smoking. Assertions that preventive measures have resulted in smoking changes that caused the decline in CHD mortality differences by age, socioeconomic status, and geographic area are based on limited available data.

Conclusion

The evidence supports the conclusion that changes in smoking habits have contributed to substantial improvement in mortality rates from the cardiovascular diseases in the United States.

Technical Notes

International Classification of Diseases

Tables A and B contain the code numbers of the International Classification of Diseases (ICD) applicable to the causes of death described in this report (*16, 20, 44, 45*). Between each revision of the ICD there are breaks in the continuity of these classifications, affecting some diseases more than others. For cardiovascular disease, the most serious breaks in continuity are between the seventh and eighth revisions and between the eighth and ninth revisions for CHD and for hypertensive disease.

The cause of death commonly referred to as coronary heart disease (CHD) was listed in both the sixth and seventh revisions of the ICD (1949–1957, 1958–1967) as "Arteriosclerotic heart disease, including coronary heart disease," code 420; in the eighth revision (1968–1978) as "Ischemic heart disease," codes 410–413; and in the ninth revision (after 1978) as "Ischemic heart disease," codes 410–414.

Expected Minus Observed Deaths

Multiplying the 1970 age-specific death rates (10-year age groups) for total cardiovascular diseases times the 1980 census gives an estimate of the number of cardiovascular disease deaths expected in 1980: 1,294,564 deaths, based on the level of mortality in 1970. An estimate of the number of cardiovascular disease deaths observed in 1980 is 1,005,692. This latter estimate is made by combining the estimated 989,000 deaths from major cardiovascular diseases in 1980 (ICD/9 codes 390–448) and the 4,803 deaths from diseases of the veins in 1980 (ICD/9 codes 451–459) (*27, 29*). The difference is 288,872 cardiovascular disease deaths "averted" in 1980 because of a decline in mortality from the level in 1970.

Multiplying the 1963 age-specific death rates (10-year age groups) for coronary heart disease (ICD/7 code 420) times the 1979 population estimate gives the number of CHD deaths, 804,000, expected in 1980, on the basis of the level of mortality in 1963 (*2, 25, 27*). The observed number of deaths from CHD in 1980 for ICD/9 codes 410–414 was 566,000, or 238,000 fewer than expected, based on the level of mortality in 1963. This procedure assumes reasonably good comparability of ICD classification of CHD in these 2 years.

Age-Adjusted Rates

Age adjustment for this Report is by the direct method. Age-specific death rates in 10-year age groups are multiplied by the "standard million" for 1940—the U.S. population by age as enumerated in that year.

TABLE A.—Codes of the 6th, 7th, 8th, and 9th revisions of the International Classification of Diseases for Selected Diagnoses

Diagnosis	1949–1967 6th and 7th revisions	1968–1978 8th revision	1979 9th revision
Cardiovascular diseases	330–334, 400–468	390–458	390–459
Coronary heart disease	420	410–413	410–414
Acute myocardial infarction	no code for this diagnosis	410	410
Other coronary heart disease	no code for this diagnosis	411–413	411–414
Cerebrovascular diseases	330–334	430–438	430–438
Hypertensive disease	440–447	400–404	401–405
Other diseases of arteries	450–456	440–448	440–448
Atherosclerosis	450	440	440
Aortic aneurysm	451	441	441
Other	452–456	442–448	442–448
All other cardiovascular disease	400–416, 421–434, 460–468	390–398, 420–429, 450–458	390–398, 415–429, 451–459
Lung cancer	162, 163	162	162
Other cancers	140–161, 164–205	140–161, 163–209	140–161, 163–208
Diabetes mellitus	260	250	250
Influenza and pneumonia	480–493	470–474, 480–486	480–487
Chronic obstructive pulmonary disease	500, 501, 527.1	490–492, 519.3	490–492, 494–496
Cirrhosis of the liver	581	571	571
Accidents, poisonings, and violence	E800–E985	E900–E999	E800–E999

SOURCE: World Health Organization (*44, 45*), National Center for Health Statistics (*20*).

TABLE B.—International classification of diseases codes for cardiovascular-renal diseases[1] and cardiovascular diseases[2], 1900–1979

Revision	Years in use	Codes
1st	1900–1909	47, 64–66, 77–86, 120, 142
2nd	1910–1920	47, 64–66, 77–85, 120, 142
3rd	1921–1929	51, 74, 75, 83, 87–90, 91b, 91c, 92–96, 129, 151
4th	1930–1938	56, 82, 90–95, 97–103, 131, 132
5th	1939–1948	58, 83, 90–103, 131, 132
6th	1949–1958	330–334, 400–468, 592–594
7th	1959–1967	330–334, 400–468
8th	1968–1978	390–458
9th	1979–	390–459

[1] Through 6th revision.
[2] After 6th revision.
SOURCE: Moriyama et al. (*16*), National Center for Health Statistics (*20*), World Health Organization (*45*).

Population Estimates

Death rates for census years and for years prior to 1961 are based on the resident or census population estimates that were available at the time the official U.S. vital statistics were prepared. Rates for 1961 to 1969, however, are based on estimates of the resident population revised to reflect the 1970 census, and rates for 1971 to 1979 are based on estimates of the resident population revised to reflect the 1980 census (*1, 2*).

References

(1) BUREAU OF THE CENSUS. Estimates of the population of the United States, by age, sex, and race: April 1, 1960 to July 1, 1973. *Current Population Reports, Population Estimates, and Projections.* U.S. Department of Commerce, Social and Economic Statistics Administration, Bureau of the Census. Series P-25, No. 519, April 1974, 79 pp.

(2) BUREAU OF THE CENSUS. Preliminary estimates of the population of the United States, by age, sex, and race: 1970 to 1981. *Current Population Reports.* U.S. Department of Commerce, Social and Economic Statistics Administration, Bureau of the Census. Series P-25, No. 917, July 1982, 65 pp.

(3) ELVEBACK, L.R. Coronary heart disease in Rochester, Minn., 1950–1975: Incidence and survivorship. In: Havlik, R.J., Feinleib, M., Thom, T., Krames, B., Sharretta, A.R., Garrison, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality,* Bethesda, Maryland, October 24–25, 1978. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication No. 79–1610, May 1979, pp. 116–122.

(4) FEINLEIB, M., THOM, T.J., HAVLIK, R.J. Decline in coronary heart disease mortality in the United States. In: Gotto, A.M., Jr., Paoletti, R. (Editors). *Atherosclerosis Reviews.* Volume 9. New York, Raven Press, 1982, pp. 29–42.

(5) FRIEDMAN, G.D. Decline in hospitalizations for coronary heart disease and stroke: The Kaiser-Permanente experience in northern California, 1971–1977. In: Havlik, R.J., Feinleib, M., Thom, T., Krames, B., Sharretta, A.R., Garrison, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality,* Bethesda, Maryland, October 24–25, 1978. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication No. 79–1610, May 1979, pp. 109–115.

(6) GARRAWAY, W.M., WHISNANT, J.P., FURLAN, A.J., PHILLIPS, L.H. II, KURLAND, L.T., O'FALLON, W.M. The declining incidence of stroke. *New England Journal of Medicine* 300(9): 449–452, March 1, 1979.

(7) GILLUM, R.F., BLACKBURN, H., FEINLEIB, M. Current strategies for explaining the decline in ischemic heart disease mortality. *Journal of Chronic Diseases* 35(6): 467–474, 1982.

(8) HAVLIK, R.J., FEINLEIB, M., THOM, T., KRAMES, B., SHARRETTA, A.R., GARRISON, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality,* Bethesda, Maryland, October 24–25, 1978. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication No. 79–1610, May 1979, 399 pp.

(9) KANNEL, W.B. Meaning of the downward trend in cardiovascular mortality. *Journal of the American Medical Association* 247(6): 877–880, February 1982.

(10) KANNEL, W.B., THOM, T.J. Implications of the recent decline in cardiovascular mortality. *Cardiovascular Medicine* 4(9): 983–997, September 1979.

(11) KLEINMAN, J.C. The potential impact of risk factor modification on coronary heart disease mortality in middle-aged men. In: *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention: Background Papers, 1979.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health and Surgeon General, DHEW Publication No. (PHS)79–55071A, 1979, pp. 187–194.

(*12*) KLEINMAN, J.C., FELDMAN, J.J., MONK, M.A. Trends in smoking and ischemic heart disease mortality. In: Havlik, R.J., Feinleib, M., Thom, T., Krames, B., Sharretta, A.R., Garrison, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* Bethesda, Maryland, October 24–25, 1978. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication No. 79–1610, May 1979, pp. 195–211.

(*13*) LEAVERTON, P. , KLEINMAN, J.C., THOM, T.J., GITTELSOHN. A.H. *Coronary Heart Disease Mortality by States.* Presented at the Annual Meeting of the Society for Epidemiologic Research, Minneapolis, June 19, 1980.

(*14*) McGEE, D., ABBOTT, R.D. *The Probability of Developing Certain Cardiovascular Diseases in Eight Years at Specified Values of Some Characteristics.* Unpublished data of Section 34 of the Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Feinleib, M. (Editor). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, March 1982.

(*15*) METROPOLITAN LIFE INSURANCE COMPANY. Recent trends in mortality from cardiovascular disease. *Statistical Bulletin* 60(2): 2–8, April-June 1979.

(*16*) MORIYAMA, I.M., KRUEGER, D.E., STAMLER, J. *Cardiovascular Diseases in the United States.* Cambridge, Harvard University Press, 1971, 496 pp.

(*17*) NATIONAL CENTER FOR HEALTH STATISTICS. *Vital Statistics of the United States, 1960.* Volume II, Mortality, Part A. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, National Vital Statistics Division, 1963.

(*18*) NATIONAL CENTER FOR HEALTH STATISTICS. *Mortality From Diseases Associated With Smoking: United States, 1950–64.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Vital Statistics. PHS Publication No. 1000, Series 20, No. 4, October 1966, 45 pp.

(*19*) NATIONAL CENTER FOR HEALTH STATISTICS. *Vital Statistics of the United States, 1965.* Volume II, Mortality, Part A. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, National Vital Statistics Division, 1967.

(*20*) NATIONAL CENTER FOR HEALTH STATISTICS. *Eighth Revision of the International Classification of Diseases Adapted for Use in the United States.* Volume 1. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of Health Research, Statistics, and Technology, DHEW Publication No. (PHS)1693, 1969, 478 pp.

(*21*) NATIONAL CENTER FOR HEALTH STATISTICS. *Mortality trend tables for leading causes and selected components, United States, 1950–1969.* (Unpublished).

(*22*) NATIONAL CENTER FOR HEALTH STATISTICS. Mortality trends: Age, color, and sex. United States—1950–1969. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, National Center for Health Statistics, DHEW Publication No. (HRA)74–1852, Series 20, No. 15, November 1973, 40 pp.

(23) NATIONAL CENTER FOR HEALTH STATISTICS. Mortality trends for leading causes of death. United States—1950–1969. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, National Center for Health Statistics. DHEW Publication No. (HRA)74–1853, Series 20, No. 16, March 1974, 75 pp.

(24) NATIONAL CENTER FOR HEALTH STATISTICS. Total serum cholesterol levels of adults 18–74 years. United States, 1971–1974. *Vital and Health Statistics.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Health Examination and Statistics, DHEW Publication No. (PHS)78–1652, Series 11, Number 205, April 1978, 31 pp.

(25) NATIONAL CENTER FOR HEALTH STATISTICS. *Chartbook for the Conference on the Decline in Coronary Heart Disease Mortality.* Comparability of cause-of-death statistics, figures and tables, and technical notes describing trends in ischemic heart disease mortality. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Vital Statistics, August 1978, 42 pp.

(26) NATIONAL CENTER FOR HEALTH STATISTICS. *Hospital Discharge Survey. 1970–1978.* (Unpublished).

(27) NATIONAL CENTER FOR HEALTH STATISTICS. *Vital Statistics—Mortality Cause of Death Summary.* Public use tapes for data years 1968–1979.

(28) NATIONAL CENTER FOR HEALTH STATISTICS. *Health, United States, 1979.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, DHEW Publication No. (PHS)80–1232, 1981.

(29) NATIONAL CENTER FOR HEALTH STATISTICS. Annual summary of births, deaths, marriages, and divorces: United States, 1980. *Monthly Vital Statistics Report.* U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, DHHS Publication No. (PHS)81–1120, Volume 29, No. 13, September 17, 1981, 31 pp.

(30) NATIONAL CENTER FOR HEALTH STATISTICS. Mortality from diseases associated with smoking: United States, 1960–77. *Vital and Health Statistics.* U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, DHHS Publication No. (PHS)82–1854, Series 20, No. 17, January 1982, 71 pp.

(31) NATIONAL CENTER FOR HEALTH STATISTICS. Utilization of short-stay hospitals: Annual summary for the United States, 1980. *Vital and Health Statistics.* U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, DHHS Publication No. (PHS)82–1725, Series 13, No. 64, March 1982, 60 pp.

(32) NATIONAL CENTER FOR HEALTH STATISTICS. Blood pressure levels and hypertension in persons ages 6–74 years: United States, 1976–80. *Advanced Data from Vital and Health Statistics.* Number 84, U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, DHHS Publication No. (PHS)82–1250, October 8, 1982.

(33) PELL, S., FAYERWEATHER, W.E. Mortality trends in myocardial infarction in a large employed population, 1975–1979. *CVD Epidemiology Newsletter* 31: 56, 1982.

(34) RICE, D.P. Statement of Dorothy P. Rice. In: *Hearings Before the Intergovernmental Relations and Human Resources Subcommittee Committee on Government Operations.* June 14, 1977. U.S. House of Representatives.

(35) STERN, M.P. The recent decline in ischemic heart disease mortality. *Annals of Internal Medicine* 91(4): 630–640, October 1979.

(36) STRONG, J.P., GUZMAN, M.A. Decrease in coronary atherosclerosis in New Orleans. *Laboratory Investigation* 43(3): 297–301, September 1980.

(37) THOM, T.J., KANNEL, W.B., FEINLEIB, M. Factors associated with the decline in coronary heart disease mortality in the United States. In: Connor, W.F., Bristow, J.D. (Editors). *Coronary Heart Disease: Complications, Prevention, and Treatment.* J.B. Lippincott Co., Philadelphia, in press.

(38) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *Arteriosclerosis 1981: Report of the Working Group on Arteriosclerosis of the National Heart, Lung, and Blood Institute.* Volume 1. Summary, Conclusions, and Recommendations. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. (NIH)82–2034, July 1981, 62 pp.

(39) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health. DHHS Publication No. (PHS)82–50179, 1982, 302 pp.

(40) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. Death rates by age, race, and sex, United States, 1900–1953: Major cardiovascular-renal diseases. *Vital Statistics Special Reports.* U.S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics, Volume 43, No. 12, July 30, 1956, pp. 187–201.

(41) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Vital Statistics of the United States, 1955.* Volume II, Mortality Data. U.S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics, 1957.

(42) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *The Health Consequences of Smoking for Women: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980, 359 pp.

(43) WEINBLATT. E., GOLDBERG. J.D., RUBERMAN. W., FRANK, C.W., MONK, M.A., CHAUDHARY, B.S. Mortality after first myocardial infarction. Search for a secular trend. *Journal of the American Medical Association* 247(11): 1576–1581, March 9, 1982.

(44) WORLD HEALTH ORGANIZATION. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.* Volume 1. Geneva, World Health Organization, 1957, 393 pp.

(45) WORLD HEALTH ORGANIZATION. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.* Volume 1. Geneva, World Health Organization, 1977, 659 pp.

(46) WORLD HEALTH ORGANIZATION. *World Health Statistics Annual.* Geneva, Switzerland. Published for each data year, 1969 to 1978.

APPENDIX B: TRENDS IN U.S. CIGARETTE USE, 1965 TO 1980

Introduction

This discussion of national trends in adult cigarette smoking over recent years in the United States includes data on prevalence, consumption, and cessation. It focuses on adult cigarette smoking patterns and cessation by age and sex cohorts. Data were drawn from an analysis of three national surveys by the National Center for Health Statistics (NCHS) and three other national surveys on adult use of tobacco conducted by the former National Clearinghouse for Smoking and Health over the period from 1965 through 1980 (*6, 7, 8*). A brief description of the data sources is presented, followed by a discussion of the data.

Surveys of Tobacco Use

The 1966 Survey on the Use of Tobacco

Two separate national probability sample surveys on adult usage of and attitudes toward tobacco conducted by the National Clearinghouse for Smoking and Health in 1966 have been combined and are treated here as a single survey.

One study design imposed a two-way stratification on all households in the continental United States, classifying each household by three types of population and nine geographic areas. The other design divided the entire area of the United States into approximately 1,700 primary sampling units (PSUs). Weighting procedures resulted in the selection of 5,770 respondents.

Within each household, the first eligible respondent (age 21 or older) was the person interviewed; all current and former smokers were also interviewed, but only a subsample of those who had never smoked was interviewed. Weighting procedures were used to bring the three groups into balance.

The 1970 and 1975 Surveys on the Adult Use of Tobacco

The 1970 and 1975 surveys sponsored by the National Clearinghouse for Smoking and Health employed the same sampling and interviewing methodologies. Where possible, questions were phrased similarly. The questionnaires for current, former, and never smokers differed slightly.

In both surveys, the sample design consisted of two parts: a national probability sample of telephone households and a national probability sample of nontelephone households.

The respondent selection procedure was designed to produce 75 percent of the interviews with "ever" smokers and 25 percent with "never" smokers. Weighting procedures were used to compensate for this oversampling of ever versus never smokers. Other weighting factors were used to adjust for age, sex, and smoker mix of the

household. The weighted number of respondents (age 21 or older) was 5,875 in 1970 and 12,079 in 1975.

Smoking Supplement to the National Health Interview Survey

The National Health Interview Survey (NHIS), a continuous nationwide sample personal household interview survey by the National Center for Health Statistics, included questions on cigarette smoking in 1965, 1966, 1970, 1974, 1976, 1977, 1978, 1979, and 1980. Information is routinely obtained on personal and demographic characteristics. Questions focused primarily on such characteristics as present smoking status, amount smoked daily, and in more recent years, attempts to quit, and on tar and nicotine levels of cigarettes smoked. Information was not obtained on opinions, attitudes, or beliefs related to smoking.

The universe for the NHIS is the civilian noninstitutionalized population of the United States. The survey is based on a multistage probability sample of primary sampling units in about 42,000 households containing about 85,000 persons. A one-third subsample of the adult respondents is interviewed for the smoking supplement (during 1965 and 1966 smoking data were obtained for all adults).

Patterns of Smoking Prevalence and Cessation

Prevalence of Cigarette Smoking

The percentage of adults who report being current regular smokers, defined as persons who have smoked at least 100 cigarettes and who were smokers at the time of interview, has been declining steadily over the last 15 years (Table 1). For the total white male population, this decline has been from 51.3 percent in 1965 to 37.1 percent in 1980, and for white females, from 34.5 to 30.0 percent. Among black adults a similar pattern was seen—for males a decline from 59.6 to 44.9 percent, and for females, from 32.7 to 30.6 percent.

Conversely, the percentage of the white adult male population who reported being former smokers increased between 1965 to 1980 from 21.2 to 31.9 percent, and of white females, from 8.5 to 16.3 percent by 1980. Again, a similar trend was observed among blacks, with the percentage of former smokers increasing from 12.6 to 20.6 percent of males, and from 5.9 to 11.8 percent of females. This increase in the percentage of former smokers is more marked among males (20.3 to 30.5 percent) than among females (8.2 to 15.7 percent), although the proportion among males increased by a factor of 1.5, while that among females doubled.

In addition to this increase in percentage of former smokers over the 15-year period, among most of the sex, race, and age groups there also appears to be an increase in the percentage of persons who

TABLE 1.—Percentage distribution of adult current and former cigarette smokers, according to sex, race, and age, in 1965, 1976, and 1980

Sex, race, and age	Current smoker[1] (percent)			Former smoker (percent)		
	1965	1976	1980[2]	1965	1976	1980[2]
MALE						
Total[3,4]						
All ages ≥ 20[5]	52.1	41.6	37.9	20.3	29.6	30.5
20–24	59.2	45.9	39.7	9.0	12.2	12.1
25–34	60.7	48.5	43.1	14.7	18.3	20.6
35–44	58.2	47.6	42.6	20.6	27.3	27.6
45–64	51.9	41.3	40.8	24.1	37.1	36.9
≥ 65	28.5	23.0	17.9	28.1	44.4	47.4
White						
All ages ≥ 20[5]	51.3	41.0	37.1	21.2	30.7	31.9
20–24	58.1	45.3	39.0	9.6	13.3	12.2
25–34	60.1	47.7	42.0	15.5	18.9	21.9
35–44	57.3	46.8	42.4	21.5	28.9	28.8
45–64	51.3	40.6	40.0	25.1	38.1	38.4
≥ 65	27.7	22.8	16.6	28.7	45.6	50.1
Black						
All ages ≥ 20[5]	59.6	50.1	44.9	12.6	20.2	20.6
20–24	67.4	52.8	45.5	3.8	4.1	10.6
25–34	68.4	59.4	52.0	6.7	11.8	11.9
35–44	67.3	58.8	44.2	12.3	13.8	21.2
45–64	57.9	49.7	48.8	15.3	28.6	26.3
≥ 65	36.4	26.4	27.9	21.5	33.0	26.6
FEMALE						
Total[3,4]						
All ages ≥ 20[5]	34.2	32.5	29.8	8.2	13.9	15.7
20–24	41.9	34.2	32.7	7.3	10.4	11.0
25–34	43.7	37.5	31.6	9.9	12.9	14.4
35–44	43.7	38.2	34.9	9.6	15.8	18.9
45–64	32.0	34.8	30.8	8.6	15.9	17.1
≥ 65	9.6	12.8	16.8	4.5	11.7	14.2
White						
All ages ≥ 20[5]	34.5	32.4	30.0	8.5	14.6	16.3
20–24	41.9	34.4	33.3	8.0	11.4	12.5
25–34	43.4	37.1	31.6	10.3	13.7	14.7
35–44	43.9	38.1	35.6	9.9	17.0	20.2
45–64	32.7	34.7	30.6	8.8	16.4	17.4
≥ 65	9.8	13.2	17.4	4.5	11.5	14.3
Black						
All ages ≥ 20[5]	32.7	34.7	30.6	5.9	10.2	11.8
20–24	44.2	34.9	32.3	2.5	5.0	2.2
25–34	47.8	42.5	34.2	6.7	8.9	11.6
35–44	42.8	41.3	36.5	7.0	9.6	12.5
45–64	25.7	38.1	34.3	6.6	11.9	14.1
≥ 65	7.1	9.2	9.4	4.5	13.3	14.1

[1] A current smoker has smoked at least 100 cigarettes and now smokes; includes occasional smokers.

[2] Final estimates. Based on data for the last 6 months of 1980.

[3] Base of percentage excludes persons with unknown smoking status.

[4] Includes all other races not shown separately.

[5] Age adjusted by the direct method to the 1970 civilian noninstitutionalized population using 5 age groups.

NOTE: Percentages do not add up to 100 because of "never smokers" in the survey population.

SOURCE: Data from the National Health Interview Survey, National Center for Health Statistics, 1965, 1976, and 1980, based on household interviews with a sample of the civilian noninstitutionalized population.

report never having smoked. In males, this is demonstrated by both races and by the age groups younger than 45 years of age. In females,

TABLE 2.—Average number of cigarettes smoked per day by current and former smokers, by sex, age, and educational level, in 1970, 1975, and 1980

Sex, age, and education	1970[1]		1975[1]		1980[2]	
	Current smoker	Former smoker	Current smoker	Former smoker	Current smoker	Former smoker
Total						
All ages ≥21	20.0	22.6	21.2	24.5	21.7	25.0
Male						
All ages ≥21	21.8	25.0	22.8	27.2	23.4	28.1
21–24	20.8	16.2	18.9	20.8	19.4	18.7
25–34	21.0	23.4	22.1	24.0	22.1	24.0
35–44	23.0	27.7	23.4	28.0	25.6	28.7
45–54	24.2	25.4	25.1	29.5	27.2	31.6
55–64	21.8	27.7	25.0	28.1	23.3	31.3
≥65	17.2	25.3	20.3	28.0	20.9	27.1
Female						
All ages ≥21	17.7	17.3	19.1	18.8	19.7	19.8
21–24	16.1	13.8	18.6	14.7	17.8	17.6
25–34	18.1	18.7	18.5	17.7	19.4	20.3
35–44	18.6	18.2	20.1	19.5	22.5	19.8
45–54	18.4	19.0	20.3	20.8	20.7	22.4
55–64	17.0	15.4	19.0	20.8	20.0	20.4
≥65	14.0	14.6	16.1	17.1	15.6	17.2
Educational level						
0–8	18.1	21.7	21.7	25.9	20.5	26.2
9–11	20.3	22.2	21.6	25.0	22.3	27.8
12	20.2	22.8	20.8	24.2	21.9	24.4
13–15	20.3	22.5	21.3	25.1	22.1	24.3
≥16	20.8	23.2	20.6	22.1	21.1	24.0

[1] National Survey on Adult Use of Tobacco, PHS, 1970.
[2] National Health Interview Survey Smoking Supplement, PHS, 1980.
NOTE: Data from 1966 National Survey were not compatible with other years.

the increase in percentage of persons who report never having smoked is limited to the age groups younger than 35 years.

Average Daily Consumption of Cigarettes

Table 2 shows data on the average number of cigarettes smoked daily during three survey periods (1970, 1975, and 1980) for both current and former smokers.

Overall, current smokers reported an increased consumption, from a mean of 20.0 cigarettes per day in 1970 to 21.7 cigarettes per day in 1980. The 1970 to 1980 increase in mean number of cigarettes smoked daily was slightly greater for females than for males (2.0 versus 1.2), a finding consistent with the increasingly similar smoking behavior in females and males. Thus, although males continue to smoke a greater average number of cigarettes per day

than do females, the difference in daily consumption between the sexes for current smokers in 1980 was less than that observed a decade earlier.

The heaviest daily consumption is observed in the middle-aged groups (35 to 64 years). A greater mean increase from 1970 to 1980 was observed among women aged 35 to 64.

Male former smokers generally reported greater daily cigarette consumption than did current smokers in each survey. This trend was not found in females. This finding is contrary to the widely held belief that those who smoke fewer cigarettes per day are more likely to quit. It may be due in part to a tendency of former smokers to overestimate their consumption and of current smokers to underestimate their consumption or both.

Among former smokers of both sexes, average daily consumption rates increased with age, peaking at the 45- to 54-year-old age category.

No trend over time is discernible by educational level in the overall mean daily consumption among current smokers. There was, however, an increase in the daily cigarette consumption of former smokers with 8 or fewer years of education, from 21.7 in 1970 to 26.2 in 1980. Within each survey year, there is also no discernible trend between level of education and daily cigarette consumption. The greater reported average daily consumption by educational status for former smokers than for current smokers may reflect cognitive dissonance, or changing social pressures that result in reporting bias.

Table 3 displays the percentage distribution of current smokers by grouped number of cigarettes smoked daily, over the 1965, 1976, and 1980 NHIS surveys. Cigarette smokers had a tendency to round off their reported number of cigarettes smoked per day (*3*) (Table 4). Approximately one-third of the smokers reported smoking exactly 20 cigarettes (one pack) a day in each of the survey years. The proportion of current smokers reporting consumption levels of 21 to 29 or 31 to 39 cigarettes per day remained relatively constant between 1970 and 1980.

Although the proportion of smokers who report consumption levels of 20 to 39 cigarettes per day has remained fairly stable over the last 10 years (48.6 vs. 49.3), a clear difference is observed at the more extreme ends of the distribution, i.e., among those smoking fewer than 20 cigarettes and those smoking 40 or more cigarettes per day.

In 1970, only 11.4 percent of the respondents reported smoking 40 or more cigarettes per day; by 1980, 16.8 percent reported smoking 40 or more cigarettes per day. During the same period, smokers reporting consumption levels of less than 20 cigarettes per day decreased from 39.8 percent in 1970 to 33.8 percent in 1980 (Table 4).

TABLE 3.—Percentage distribution of adult current smokers[1] by grouped number of cigarettes smoked per day by sex, race, and age, 1965, 1976, and 1980

Sex, race, and age	Cigarettes smoked per day								
	<15			15–24			≥25		
	1965	1976	1980[2]	1965	1976	1980[2]	1965	1976	1980[2]
MALE									
Total[3,4]									
All ages ≥ 20	28.3	24.2	23.1	46.3	44.8	42.7	25.4	31.0	34.1
20–24	34.9	31.6	32.0	49.7	49.9	47.8	15.4	18.5	20.2
25–34	25.7	25.5	23.6	50.0	45.8	46.5	24.3	28.7	29.9
35–44	23.7	19.6	15.8	44.8	41.2	42.3	31.5	39.2	41.9
45–64	26.7	18.5	21.6	45.3	44.1	36.4	28.0	37.4	42.0
≥ 65	47.1	39.1	29.2	39.0	42.7	46.1	13.8	18.2	24.7
White									
All ages ≥ 20	25.9	21.4	19.1	46.8	44.9	43.6	27.4	33.7	37.4
20–24	32.3	27.5	27.1	50.8	52.8	50.4	16.9	19.7	22.4
25–34	22.8	22.1	19.5	51.1	46.5	47.4	26.1	31.4	33.1
35–44	21.3	17.2	12.8	44.8	40.4	42.1	33.9	42.5	45.1
45–64	24.6	16.2	17.3	45.4	43.3	37.4	30.0	40.4	45.3
≥ 65	44.6	37.5	26.1	40.3	42.2	46.2	15.1	20.4	27.7
Black									
All ages ≥ 20	48.1	43.8	48.7	42.6	44.8	40.3	9.3	11.5	10.9
20–24	52.7	56.9	56.6	41.9	34.2	36.7	5.3	8.9	6.8
25–34	47.8	46.0	44.4	41.7	43.5	46.2	10.5	10.5	9.6
35–44	42.5	38.5	45.6	45.5	44.8	41.1	12.0	16.7	13.2
45–64	46.9	35.9	51.1	43.7	50.8	35.0	9.4	13.3	14.1
≥ 65	64.9	53.0	41.7	31.9	47.0	47.2	3.2		11.1
FEMALE									
Total[3,4]									
All ages ≥ 20	43.6	36.5	34.2	42.2	43.8	42.0	14.2	19.6	23.7
20–24	48.4	43.1	42.8	41.9	42.4	41.1	9.7	14.5	16.1
25–34	41.4	34.3	33.5	43.1	45.2	41.9	15.5	20.5	24.6
35–44	39.1	33.8	27.8	43.7	44.4	39.3	17.1	21.8	33.0
45–64	44.4	34.3	29.8	42.0	44.2	45.9	13.6	21.5	24.2
≥ 65	62.6	49.3	48.9	31.0	38.9	37.7	6.4	11.8	13.4
White									
All ages ≥ 20	41.0	33.2	30.6	43.9	45.2	43.8	15.1	21.6	25.6
20–24	45.3	39.3	37.4	44.4	44.3	44.1	10.4	16.4	18.5
25–34	37.9	30.6	28.6	45.4	46.8	44.9	16.7	22.6	26.5
35–44	36.2	29.5	24.6	45.3	45.4	39.9	18.4	25.1	35.5
45–64	42.4	32.0	26.4	43.2	45.1	47.8	14.5	23.0	25.9
≥ 65	61.5	45.7	48.1	31.8	41.7	37.7	6.8	12.6	14.2
Black									
All ages ≥ 20	67.7	60.0	61.1	26.4	33.8	28.9	5.9	6.1	10.0
20–24	73.4	65.7	78.0	22.1	31.3	22.0	4.5	3.0	-
25–34	66.2	58.8	61.9	25.1	33.6	22.0	8.7	7.7	16.2
35–44	63.4	60.4	55.6	30.4	38.1	35.6	6.2	1.4	8.8
45–64	69.4	53.2	53.8	26.9	36.7	34.2	3.6	10.1	12.0
≥ 65	83.2	100.0	66.3	16.8	-	34.7	-	-	-

[1] A current smoker has smoked at least 100 cigarettes and now smokes; includes occasional smokers.

[2] Based on data for the last 6 months of 1980.

[3] Base of percentage excludes unknown amount smoked.

[4] Includes all races not shown separately.

SOURCE: Data from the National Health Interview Survey, National Center for Health Statistics, 1965, 1976, and 1980, based on household interviews with a sample of the civilian noninstitutionalized population.

TABLE 4.—Percentage distribution of adult current smokers who reported smoking specific numbers of cigarettes per day, in 1970, 1975, and 1980

Number of cigarettes/day	Percentage of current smokers		
	1970[1]	1975[1]	1980[2]
1–9	15.8	13.5	13.1
	39.8	37.0	33.8
10–19	24.0	23.5	20.7
20	34.9	32.0	34.8
21–29	3.1	2.8	2.3
30	9.6	12.1	11.5
31–39	1.0	0.8	0.7
40	8.8	10.7	11.1
	11.4	15.2	16.8
41+	2.6	4.5	5.7

[1] National Survey on Adult Use of Tobacco, PHS, 1970 and 1975.
[2] National Health Interview Survey Smoking Supplement, PHS (Preliminary), 1980.
NOTE: Data from 1966 National Survey are not compatible with other years.

These findings may be due to several factors, including (1) increased smoking (possibly among those who have switched to lower tar cigarettes), (2) a higher cessation rate among persons smoking fewer cigarettes, (3) the entry of new smokers of greater numbers of cigarettes, or (4) some combination of these factors.

Number of Attempts to Quit Smoking

Survey data have shown that the majority of current smokers have made at least one serious but unsuccessful attempt to quit (*4*).

Table 5 shows the percentage of current smokers who reported having made three or more attempts to quit. Similar data are shown for former smokers for two of the survey years. A modest downward trend is observed in the percentage of current smokers who reported making three or more attempts to quit (from 41.2 percent in 1966 to 38.7 percent in 1980), but the proportion of former smokers reporting three or more attempts to quit increased from 36.0 percent to 53.2 percent over the period from 1966 to 1975; this increase is seen in most of the sex, race, and age groups.

Comparing the proportion of current smokers who had made three or more attempts to quit by years of education showed a general downward trend over time for all education levels except in the less than 8 years of education group, where the proportion increased from 38.9 percent in 1966 to 47.0 percent in 1980. Among the most educated current smokers, the decline was from 59.8 to 39.4 percent.

TABLE 5.—Percentage of current and former smokers who made three or more attempts to quit, by sex, age, and educational level, in 1966, 1975, and 1980

Sex, age, and education	1966[1] Current smoker	1966[1] Former[3] smoker	1975[1] Current smoker	1975[1] Former[3] smoker	1980[2] Current smoker	1980[2] Former[4] smoker
Total						
All ages ≥21	41.2	36.0	40.5	53.2	38.7	
Male						
All ages ≥21	40.7	36.9	39.4	55.1	38.8	
21–24	35.4	21.5	39.0	50.0	31.5	
25–34	37.4	50.0	38.2	43.7	38.7	
35–44	41.8	36.6	37.1	48.8	35.0	
45–54	42.9	36.8	44.1	58.4	39.8	
55–64	44.1	34.1	45.6	63.3	42.8	
≥65	46.9	30.1	31.0	61.9	52.6	
Female						
All ages ≥21	41.5	34.0	42.0	49.1	38.7	
21–24	28.6	35.3	32.3	52.9	31.3	
25–34	34.5	38.1	39.5	47.2	31.0	
35–44	43.5	33.3	45.1	42.7	42.5	
45–54	56.7	23.9	44.8	57.0	37.1	
55–64	38.6	43.6	44.7	50.9	49.2	
≥65	43.5	28.6	46.9	46.4	46.1	
Educational level						
0–8	38.9	32.3	44.3	58.5	47.0	
9–11	42.7	30.0	40.8	53.6	38.4	
12	38.4	39.2	40.0	56.3	37.2	
13–15	37.7	42.8	38.4	46.8	35.2	
≥16	59.8	36.8	41.4	52.2	39.4	

[1] National Survey on Adult Use of Tobacco, PHS, 1966 and 1975.
[2] National Health Interview Survey Smoking Supplement, PHS (Preliminary), 1980.
[3] Includes the last successful attempt.
[4] 1980 former smoker data not available.

Recent Attempt to Quit

Data in Table 6 show the percentage of current and former smokers who reported an attempt to quit in the 12 months prior to the interview. Although there was little change overall from 1966 to 1975 in the percentage of current smokers who reported making an attempt to quit smoking in the previous year (1.5 percent), from 1975 to 1980 there was an increase of almost 10 percent. This increase is shown consistently for all the sex, race, and age groups. Among those who had attempted to quit, proportionately more young persons (under 35 years) than older persons reported attempting to quit during the previous 12 months.

TABLE 6.—Percentage of current and former smokers who attempted to quit during the last year, by sex, age, and educational level, in 1966, 1975, and 1980

Sex, age, and education	1966[1] Current smoker	1966[1] Former smoker	1975[1] Current smoker	1975[1] Former smoker	1980[2] Current smoker	1980[2] Former smoker[3]
Total						
All ages ≥21	26.0	13.8	27.5	9.8	36.7	
Male						
All ages ≥21	23.3	12.1	25.5	8.2	33.4	
21–24	44.0	6.7	44.0	29.2	52.5	
25–34	28.8	20.4	28.7	15.8	37.3	
35–44	19.4	11.2	19.1	6.3	26.9	
45–54	19.1	14.8	20.0	7.0	27.3	
55–64	12.2	13.1	25.3	1.9	29.9	
≥65	15.6	1.8	19.3	3.1	29.2	
Female						
All ages ≥21	29.4	17.2	30.0	12.7	40.6	
21–24	40.0	33.3	50.8	27.5	55.1	
25–34	35.7	24.2	33.0	20.3	47.1	
35–44	25.0	12.5	29.1	11.7	39.5	
45–54	25.2	13.0	19.8	9.3	30.0	
55–64	17.9	11.4	23.6	6.4	31.8	
≥65	27.8	17.9	25.2	4.2	37.0	
Educational level						
0–8	25.4	12.1	27.6	4.2	36.7	
9–11	25.9	15.5	28.0	9.9	38.8	
12	26.8	15.1	26.1	10.0	37.7	
13–15	25.0	10.2	29.1	13.4	31.3	
≥16	26.1	15.5	27.5	9.3	38.4	

[1] National Survey on Adult Use of Tobacco, PHS, 1966 and 1975.
[2] National Health Interview Survey Smoking Supplement, PHS (Preliminary), 1980.
[3] 1980 former smoker data not available.

Relationship of Tar Yields to Smoking Behavior

In 1972, the Public Health Service classified tar as one of the "most likely" contributors to the health hazards posed by cigarettes, and studies have confirmed its carcinogenicity (*4*). In response to this finding, a major change occurred in the cigarette products manufactured and actually used. Over the last two decades, the proportion of domestically consumed cigarettes yielding 15 mg or less of tar has increased from 15 percent in 1968 to 60.9 percent in 1981 (*7*).

The cigarette industry has also increased its promotional activities in marketing brands yielding 15 mg or less tar. The percentage of dollars expended in the United States on advertising and promotion of cigarettes yielding 15 mg or less tar has increased from 19.6 percent in 1975 to 48.1 percent in 1978. These factors may account,

TABLE 7.—Percentage distribution of current regular smokers by tar level of primary brand of cigarettes, by sex and age, in 1975 and 1980

Sex and age	1975[1] Tar level					1980[2] Tar level				
	<5 mg	5–9 mg	10–14 mg	15–19 mg	20+ mg	<5 mg	5–9 mg	10–14 mg	15–19 mg	20+ mg
Total										
All ages ≥21	0.8	0.6	9.5	67.9	20.2	6.3	13.1	25.4	44.8	10.4
Male										
All ages ≥21	0.5	0.6	9.5	63.5	25.8	4.1	10.6	22.5	49.5	13.3
21–24	—	—	8.4	79.0	12.6	2.6	8.1	22.2	66.0	1.0
25–34	0.5	0.8	10.3	70.5	17.9	3.9	10.2	23.7	58.4	3.7
35–44	1.1	0.2	8.5	65.8	24.4	3.8	10.9	25.3	45.0	14.9
45–54	—	0.5	12.1	56.1	31.3	5.0	10.1	22.2	39.0	23.6
55–64	1.2	1.6	8.5	50.2	38.5	5.4	11.6	19.6	39.8	23.6
≥65	0.4	0.8	6.7	49.3	42.7	3.7	15.5	16.2	38.3	26.3
Female										
All ages ≥21	1.1	0.6	11.7	73.2	13.4	8.9	15.9	28.7	39.4	7.1
21–24	1.2	0.3	11.7	80.4	6.4	5.5	8.5	32.5	51.9	1.7
25–34	0.6	0.4	10.9	78.4	9.7	6.7	18.9	28.9	44.5	0.9
35–44	1.2	0.9	13.0	74.6	10.3	13.6	15.2	29.1	37.1	5.1
45–54	1.5	0.3	10.8	65.6	21.9	8.1	17.8	29.9	32.5	11.7
55–64	0.8	—	12.6	70.3	16.3	9.7	13.7	24.2	37.6	14.9
≥65	2.1	3.1	12.5	63.9	18.5	9.6	18.6	26.6	30.2	14.9

[1] National Survey on Adult Use of Tobacco, PHS, 1975.
[2] National Health Interview Survey Smoking Supplement, PHS (Preliminary), 1980.

in part, for the ever-increasing use by current smokers of lower tar cigarettes.

The definition of cigarettes as "lower tar" at 15 mg is arbitrary. Nonetheless, this breakpoint has gained general acceptance. Special note should be taken, however, that tar yields vary continuously, and groupings by relative yield measurements do not automatically imply differences in either the type or the magnitude of their biological effects.

The percentage distribution of current regular smokers by tar level of their primary brand of cigarette is presented in Table 8. A clear trend toward increased use of lower tar products is apparent.

The 1975 data on brands were coded to the 1975 Federal Trade Commission (FTC) values for tar yield, and the 1980 data were coded to the 1979 FTC values. As tar values have been progressively declining, the 1980 data probably represent slightly higher values of tar yields than were actually being used at that time.

Conclusions

1. The proportion of current regular smokers declined steadily between 1965 and 1980. The decline was steeper among males (from 52.1 to 37.9 percent) than among females (from 34.2 to 29.8 percent).
2. The proportion of never smokers increased steadily from 1965 to 1980 among males (27.6 to 31.6 percent), except those 45 years old and older. Among females, only 20- to 34-year-olds showed an increase in proportion of never smokers.
3. The mean number of cigarettes smoked per day by current smokers increased slightly from 1970 to 1980 (from 20 to 21.7 cigarettes).
4. Males smoked a higher mean number of cigarettes throughout the 1970–1980 period, but the number for males and females increased about the same amount.
5. Heaviest daily consumption was in the middle-aged group (35–65 years). The greatest mean increase was observed among women aged 35 to 44.
6. The proportion of current smokers who smoked less than 20 cigarettes per day decreased between 1970 and 1980 (39.8 to 33.8 percent); the proportion smoking one pack exactly (20 cigarettes) remained constant (34.9 to 34.8 percent); the proportion smoking from 21 to 39 cigarettes increased slightly (13.7 to 14.5 percent); and the proportion smoking two or more packs per day increased (11.4 to 16.8 percent).
7. The proportion of current smokers who attempted to quit three or more times decreased slightly from 1966 to 1980 (41.2 to 38.7 percent).
8. The proportion of former smokers having made three or more attempts to quit increased sharply (36 to 53.2 percent) from 1966 to 1975.
9. The proportion of current smokers who had attempted to quit during the past year increased from 1966 to 1980 (26.0 to 36.7 percent).
10. Among current smokers, younger persons and females were more likely than older persons and males to have attempted to quit during the previous 12 months.
11. The proportion of former smokers who had attempted to quit during the previous 12 months decreased from 1966 to 1975 (13.8 to 9.8 percent).
12. Among former smokers, younger persons and females were more likely than older persons and males to have quit during the previous 12 months.

References

(*1*) MAXWELL, J.C., Jr. Maxwell estimates 1981 cigarette sales up 2.6 percent. *United States Tobacco Journal* 209(23–24): 1, 6, 8, 50, December 8–22, 1981.

(*2*) NATIONAL CENTER FOR HEALTH STATISTICS. *Health, United States, 1981.* U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, National Center for Health Services Research, DHHS Publication No. (PHS)82–1232, December 1981, 337 pp.

(*3*) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Changing Cigarette: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHHS Publication No. (PHS)81–50156, 1981, 252 pp.

(*4*) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79–50066, 1979, 1136 pp.

(*5*) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *The Health Consequences of Smoking for Women: A Report of the Surgeon General.* U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980, 359 pp.

(*6*) U.S. PUBLIC HEALTH SERVICE. *Use of Tobacco, Practices, Attitudes, Knowledge, and Beliefs, United States: Fall 1964 and Spring 1966.* U.S. Department of Health, Education, and Welfare, National Clearinghouse for Smoking and Health, July 1969, 807 pp.

(*7*) U.S. PUBLIC HEALTH SERVICE. *Adult Use of Tobacco, 1970.* U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Clearinghouse for Smoking and Health, DHEW Publication No. (HSM)73–8727, June 1973, 129 pp.

(*8*) U.S. PUBLIC HEALTH SERVICE. *Adult Use of Tobacco, 1975.* U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Clearinghouse for Smoking and Health, June 1976.

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